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## CONTRIBUTORS TO THIS NUMBER

W Osler Abbott, M D , F.A.C.P., Assistant Professor of Medicine, School of Medicine, University of Pennsylvania, Ward Physician, Hospital of the University of Pennsylvania.

Frederick K Albrecht, M D , Passed Assistant Surgeon, U S Public Health Service, U S Marine Hospital, Baltimore, Maryland

William Dale Beamer, M D , Ross V Patterson Fellow in Physiology and Gastro enterology, Jefferson Medical College

Alson E. Braley, M D , Assistant Professor Department of Ophthalmology, College of Physicians and Surgeons, Columbia University, and Assistant Attending Surgeon, Vanderbilt Clinic and Presbyterian Hospital, New York City

Charles C Chapple, M D , Associate in Pediatrics School of Medicine, University of Pennsylvania Associate Pediatrician Hospital of the University of Pennsylvania and the Children's Hospital of Philadelphia

Charles William Dunn M D , F.A.C.P., Associate in Medicine Graduate School of Medicine, University of Pennsylvania, Endocrinologist, Graduate Hospital of the University of Pennsylvania and Abington Memorial Hospital

Harrison F Flippin, M D , F.A.C.P., Associate in Medicine, Schools of Medicine, University of Pennsylvania, Ward Physician Philadelphia General Hospital and Hospital of the University of Pennsylvania

William I Gifter, M D Clinical Instructor in Medicine Women's Medical College, Philadelphia, Assistant Ward Physician, Philadelphia General Hospital

Reynold S Griffith, M D., Assistant Professor of Medicine Jefferson Medical College Assistant Physician Jefferson Hospital

John H Hodges M D Fellow in Medicine Jefferson Medical College

Boland Hughes M D, Associate in Urology School of Medicine University of Pennsylvania Chief of Clinic Urological Service Hospital of the University of Pennsylvania

## CONTRIBUTORS TO THIS NUMBER

Douglas W Lund, M D , Department of Medicine, Jefferson Medical College

Guy M Nelson, M D , Assistant Professor of Medicine, Jefferson Medical College, Assistant in Medicine, Jefferson Hospital

William Harvey Perkins, M D , Sc D , Dean and Professor of Preventive Medicine, Jefferson Medical College, Attending Physician, Jefferson Medical College Hospital

Alison H. Price, M D , Ross V Patterson Fellow in Medicine, Jefferson Medical College and Hospital

John G Reinhold, Ph D , Principal Biochemist, Philadelphia General Hospital

Edward A Schumann, M D , F A C S , Surgeon-in-Chief, Kensington Hospital for Women, Chief of Service in Gynecology and Obstetrics, Protestant Episcopal Hospital

Edward Weiss, M D , F A C P , Professor of Clinical Medicine, Temple University Medical School

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## Erratum

In the second prescription given on page 1395 of the preceding issue (Boston Number), substitute the words "Tincture of Belladonna" for "Atropine Sulfate"

# THE MEDICAL CLINICS of NORTH AMERICA

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## *Philadelphia Number*

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### SULFAMERAZINE CLINICAL EVALUATION IN 400 CASES\*

HARRISON F. FLIPPIN, M.D., F.A.C.P.,† JOHN G. REINHOLD, Ph.D.‡  
and  
WILLIAM I. GEFTER, M.D.‡

It is generally recognized that sulfadiazine, by virtue of its equal or superior antibacterial efficacy and its relatively low toxicity, is the most satisfactory of the sulfonamide compounds now in common use. Despite these attributes, sulfadiazine is not an ideal chemotherapeutic agent since certain shortcomings are apparent: (1) the drug is slowly absorbed from the gastrointestinal tract<sup>1</sup> and (2) at times it gives rise to serious toxic reactions, particularly in the urinary tract.<sup>2</sup> Attempts to find a drug possessing definite superiority for clinical use over sulfadiazine have directed attention to the methyl derivatives of

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\* From the Philadelphia General Hospital Committee for the Study of Pneumonia, which also includes J. H. Clark, M.D. and S. Brandt Rose, M.D. The authors are indebted to Mrs. Rose Polowsky Feldman for technical assistance.

† Associate in Medicine, Schools of Medicine, University of Pennsylvania; Ward Physician, Philadelphia General Hospital and Hospital of the University of Pennsylvania.

‡ Principal Biochemist, Philadelphia General Hospital.

§ Clinical Instructor in Medicine, Women's Medical College, Philadelphia; Assistant Ward Physician, Philadelphia General Hospital.

Of these, sulfamerazine has warranted clinical trial because of its therapeutic effectiveness against experimental infections, its pharmacologic behavior, and its relatively low toxicity in animals. This report includes a brief review of the chemical and pharmacological data pertaining to sulfamerazine and presents the results of our clinical experience with its use in the treatment of a variety of acute infections.

### Sulfamerazine

Sulfamerazine (2-sulfanilamido-4-methyl-pyrimidine, sulfamethyldiazine), synthesized by two groups of investigators,<sup>3, 4</sup> is one of the methyl homologues of sulfadiazine. The structural formulas of sulfadiazine and sulfamerazine are shown in Figure 142

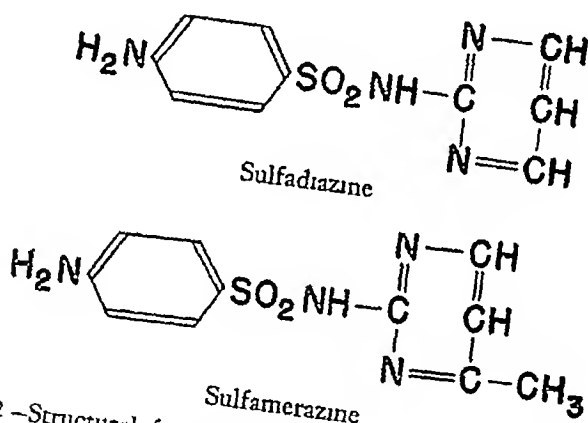


Fig 142—Structural formulas of sulfadiazine and sulfamerazine.

### ANIMAL EXPERIMENTS

The therapeutic activity of sulfamerazine was described by Roblin, Williams, Winnek and English<sup>3</sup> at the same time that they reported on that of sulfadiazine. It was found that both of these drugs were considerably more active against streptococcal pneumococcal and staphylococcal infections in mice than sulfanilamide, sulfapyridine, or sulfathiazole. Pharmacologic studies by Welch, Mattus, Latven, Benson and Shiels<sup>5</sup> in various species of laboratory animals have indicated that sulfamerazine is more rapidly and more completely absorbed from the gastrointestinal tract and more slowly excreted by the kidney than is sulfadiazine. Toxicologic observations by this same group of

workers suggested that sulfamerazine is no more toxic in experimental animals than is sulfadiazine, when a comparison is made on the basis of blood concentration of the drugs. In these toxicity experiments, particular attention was given to the possibility of neuropathologic changes, because of past clinical experience with the sulfonamides containing a methyl group (sulfamethylthiazole, sulfanilyl dimethylsulfanilamide).<sup>6</sup> It was

### FREE DRUG LEVEL

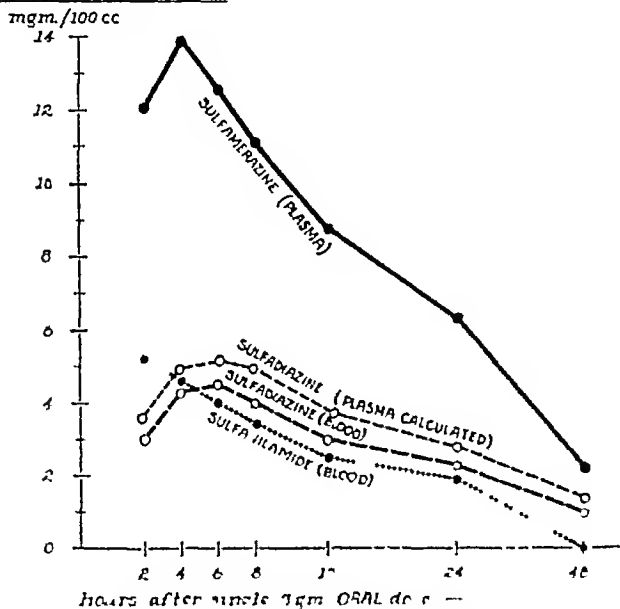


Fig. 143. Average levels of free drug after single oral 3-gm dose of sulfanilamide, sulfadiazine, and sulfamerazine.

found that dogs or monkeys, given large doses of sulfamerazine over thirty-day periods showed no evidence of nerve injury but chickens with high blood concentration of the drug developed definite nerve lesions although the changes were no greater than those resulting from lower blood levels of sulfadiazine in the same species.



## ABSORPTION, DISTRIBUTION AND EXCRETION STUDIES

Oral administration of a single dose of 3 gm of sulfamerazine is followed by a rapid rise in its concentration in plasma to higher levels that are sustained for a longer period of time<sup>8 5 7</sup> than after ingestion of the same amount of sulfadiazine<sup>1</sup> (Fig 143) Patients receiving 1 gm every four hours after the initial 3-gm dose maintained an average plasma concentration of sul-

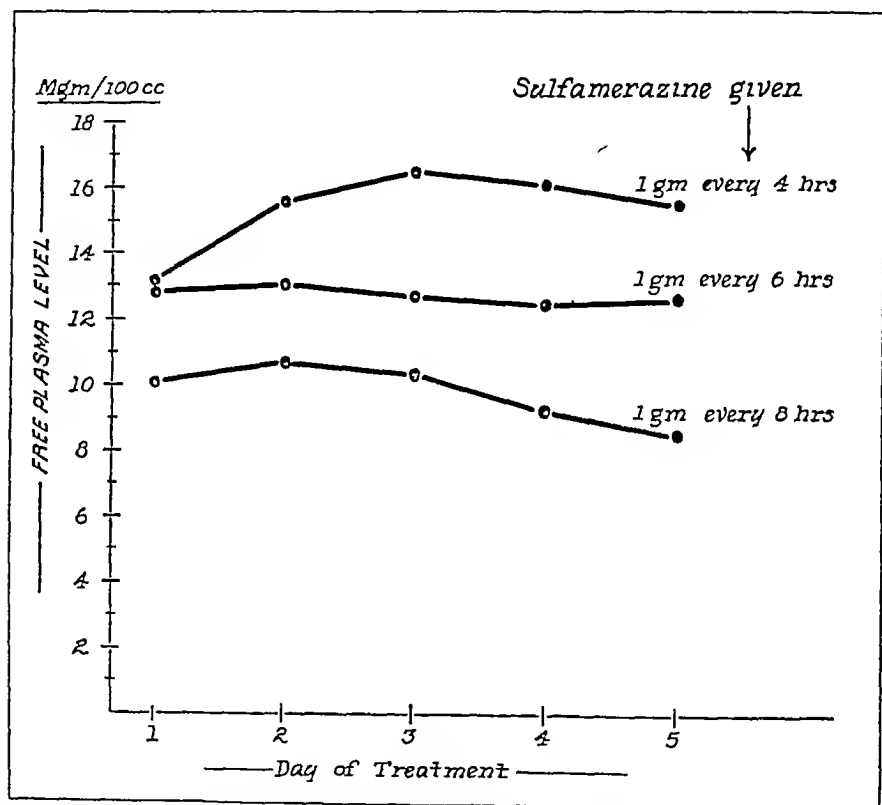


Fig 144—Average daily plasma levels of free drug in patients receiving sulfamerazine therapy

famerazine (free) of 15.4 mg per 100 cc, those who received 1 gm every six hours, 12.7 mg per 100 cc, and those who received 1 gm every eight hours, 10.9 mg per 100 cc (Fig 144) Acetylation occurred to the same extent as with sulfadiazine, an average of about 15 per cent of the total concentration of sulfamerazine in plasma being present in acetylated form<sup>9</sup> Sulfamerazine resembles sulfathiazole in that the erythrocytes contain much lower concentrations than the plasma.<sup>8 7</sup> For this

reason determinations on serum or plasma are more informative than those made on whole blood

In cerebrospinal, pleural and ascitic fluids concentrations of sulfamerazine appear to be comparable to those of sulfadiazine, however, more data are needed. In a group of patients suffering from meningitis and being treated with sulfamerazine, the ratio of the sulfamerazine concentration in cerebrospinal fluid to that in plasma averaged 0.42 and ranged from 0.23 to 0.66 so that wide variations occurred<sup>9</sup> in cerebrospinal fluid concentration. An apparent correlation between concentration of sulfamerazine in cerebrospinal fluid and response of meningococcal meningitis was not substantiated by application of statistical analysis.<sup>9</sup>

The higher concentrations of sulfamerazine in blood, compared with other sulfonamides, is in part due to more complete absorption from the gastro-intestinal tract and in part due to the slower rate of excretion.<sup>10</sup> Sulfamerazine and its acetyl derivative are more soluble in urine than are the corresponding forms of sulfadiazine. Increasing the urine pH from 6 to 7 nearly doubles the solubility of both free sulfamerazine and acetyl sulfamerazine.<sup>11</sup> Because of the greater solubility and smaller amounts required to produce a given blood level and therapeutic response, the likelihood of crystal and concretum formation in the urinary tract is distinctly less than with sulfadiazine. However, the smaller intake of drug is offset to some extent by the more complete absorption of sulfamerazine.

#### CLINICAL MATERIAL AND METHODS

The response to treatment of the first 400 patients who received sulfamerazine\* for at least twelve hours has been evaluated. The patients were studied at the Philadelphia General Hospital and the Hospitals of the University of Pennsylvania. The results have been included in part in recent reports from these institutions.<sup>7, 10, 11, 12</sup> In general, the drug was given orally with an initial dose of 3 gm. followed by 1 gm. every four, six, or eight hours depending on the nature of the infection until the temperature had remained normal for forty-eight to seventy-two hours. In severe infections such as meningitis, encephalitis or peritonitis the initial dose of 3 gm. was followed

\*Sharp and Doherty Laboratories, Cheltenham, Pa. The following manufacturers are used in this study:

administered by vein (5 per cent solution of sulfamerazine sodium in distilled water) and followed by 1 gm. by mouth every four hours. All pneumonia cases received the same initial dose by mouth, followed by 1 gm. every eight hours, excepting the first twenty-three patients who received 1 gm. every six hours. Patients with urinary tract infections received 2 gm. of the drug daily at twelve-hour intervals in equal, divided doses. Infants and children received similar treatment with proportionately smaller dosages. With the exception of ten patients with gonococcal urethritis, all of the patients were hospitalized and were closely followed with appropriate laboratory studies. Fluids were given liberally, usually from 2000 to 3000 cc. a day, but none of the patients received alkalis.

## RESULTS OF SULFAMERAZINE THERAPY

### Pneumococcal Infections

*Pneumonia*—During the course of this study, 199 adult patients with pneumococcal pneumonia were treated with sulfamerazine, of these, thirteen died (6.5 per cent mortality). In this group, thirty-four (17 per cent) had positive blood cultures and ten of these bacteremic patients died (29 per cent). Complications in this series of cases were relatively few. Two patients developed empyema, both recovering following thoracotomy. Endocarditis occurred in two patients, both of whom died. Two patients developed pneumococcal meningitis and these have been included in the meningitis group. The average total dosage for the successfully treated patients was 22.9 gm., given over a period averaging 6.4 days. Eight patients received specific serum and two received penicillin in addition to sulfamerazine.

As in former studies of the therapeutic effectiveness of sulfonamides in the treatment of pneumonia at the Philadelphia General Hospital, the medical services were so divided that the number of pneumonia patients receiving sulfamerazine was equal to that of a control group treated with sulfadiazine at the same time. The results<sup>12</sup> showed that the effects of the two drugs on final mortality were approximately the same, 7.5 per cent in the group of eighty adult patients treated with sulfamerazine as compared with 10 per cent in the group which received sulfadiazine. Sulfamerazine tended to lower the tem-

perature somewhat more rapidly than did sulfadiazine, however the duration of chemotherapy and the incidence of complications were essentially the same for the two groups

TABLE 1

SUMMARY OF RESULTS OF SULFAMERAZINE IN 400 CASES

Causative Agent	Disease	Number of Patients	Died	Per Cent Died
Pneumococcus	Pneumonia	199 (34)	13 (10)	6.5 (29.4)
	Meningitis	12 (7)	10 (5)	83.3 (71.4)
	Peritonitis	2	0	0
Meningococcus	Meningitis	99 (13)	5 (1)	5.1 (7.6)
	Meningococemia	(1)	0	0
Streptococcus haemolyticus	Pharyngitis	4	0	0
	Pneumonia	2	0	0
	Endocarditis—acute	(1)	(1)	(100.0)
	Cellulitis	2	0	0
	Erysipelas	1	0	0
	Lymphangitis	2	0	0
	Sinusitis	1	0	0
	Otitis media—acute	1	0	0
	Meningitis	(1)	0	0
Streptococcus viridans	Endocarditis—sub-acute	(4)	(1)	(100.0)
Staphylococcus aureus	Endocarditis—acute	(1)	(1)	(100.0)
	Furunculosis	1	0	0
Hemophilus influenzae	Meningitis	5	2	40.0
Mycobacterium tuberculosis	Pneumonia	3	3	100.0
	Meningitis	6	6	100.0
Gonococcus	Urethritis (male)—acute	10	0	0
Virus?	Primary atypical pneumonia	15	0	0
	Lymphocytic choriomeningitis	3	0	0
	Encephalitis	2	0	0
Unspecified	Bronchopneumonia	11	1	9.0
	Urinary tract	11	0	0

( )—Inactive Host-Culture

*Pneumococcal Meningitis*—Sulfamerazine was used in the treatment of twelve adult patients with pneumococcal meningitis.

gitis with ten deaths (83 per cent mortality) In the fatal cases, four patients were moribund on admission to the hospital and died within twenty-four hours Two cases complicated pneumonia, one patient developed endocarditis, and another, a seventy-five-year-old male, died on the second day of treatment The remaining two patients responded initially to the drug but failed to recover Five of these patients received specific serum along with sulfamerazine and a single patient was given penicillin in addition In the two successfully treated cases only the drug was given, although in one a radical mastoidectomy was definitely instrumental in the patient's recovery<sup>13</sup> The mortality of 83 per cent obtained in this small series of cases does not compare well with the results recently reported by Hodes, Smith and Ickes<sup>14</sup> in which sixty cases of the disease were treated with sulfonamides with thirty-five deaths (58 per cent mortality), although other investigators<sup>15, 16, 17</sup> in this field are of the belief that the present mortality of pneumococcal meningitis in unselected cases is in the vicinity of 80 per cent after all available methods of treatment are employed

*Peritonitis*—Two cases of pneumococcal peritonitis were successfully treated with sulfamerazine In both instances the diagnosis was made following laparotomy for suspected rupture of an abdominal viscus with resultant peritonitis

### Meningococcal Infections

*Meningitis*—Within the period of this study, meningococcal meningitis was epidemic in Philadelphia and provided ample opportunity to test the efficacy of sulfamerazine Ninety-nine cases of the disease were treated with this drug with five deaths (5 per cent mortality) In this group there were fifteen patients in whom the diagnosis of meningococcal meningitis was based on a typical clinical picture, increased spinal fluid pressure, and a turbid cerebrospinal fluid with a high polymorphonuclear cell count, but without conclusive bacteriological evidence We believe these represent true cases of the disease and have therefore included them If the patients in this subgroup are excluded, however, the corrected mortality becomes 6 per cent Positive blood cultures were obtained in 13 per cent of the cases with one death (8 per cent mortality) In the fatal cases, two patients were moribund on admission to the hospital and died within

twenty-four hours, one had a right-sided torticollis of cerebral origin at the time treatment was started, and, although he received 105 gm of sulfamerazine, he finally died. Postmortem studies revealed areas of recent softening in the globus pallidus but no gross evidence of meningitis. The remaining two deaths occurred in patients in whom treatment was started late in the disease. For the successfully treated group, definite clinical improvement, manifested mainly by mental clarity, was apparent within forty-eight hours of drug therapy in approximately 70 per cent of the cases, although fever usually persisted for several days following the initial response. The average time observed before the recovered group became afebrile was five to six days.

Six of the patients received intrathecal meningococcal serum in addition to sulfamerazine. Of these, one died. It is our feeling from observation of the clinical response in these cases that the same results would have probably been obtained without the use of the serum. One patient responded poorly to sulfamerazine, but made a brilliant recovery after the use of penicillin. Complications of the disease were observed in 15 per cent of the patients. These consisted of arthritis (six cases), ocular palsies (seven cases), Bell palsy (one case), and deafness (one case). Although eight of these complications were present on admission, all were transient, and recovery was complete. These results compare favorably with those recently reported from the Philadelphia General Hospital in which sulfadiazine was employed (12.5 per cent mortality).<sup>15</sup>

A single case of meningococcemia (without associated meningitis) was treated successfully with sulfamerazine.

#### Streptococcal and Staphylococcal Infections

Fifteen cases of hemolytic streptococcal infections of various types were treated with satisfactory recovery in all except for one patient with an acute hemolytic streptococcal endocarditis.

Four patients with subacute bacterial endocarditis with *Streptococcus viridans* bacteremia were treated unsuccessfully.

One patient with acute *Staphylococcus aureus* endocarditis failed to recover. A satisfactory therapeutic result was obtained in a single case of furunculosis of the external auditory canal due to *Staphylococcus aureus*.

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### Influenzal Infections

There were five cases of influenzal meningitis due to the *Hemophilus influenzae* bacillus, with two deaths (40 per cent mortality). Two of the three recovered patients received appropriate serum therapy which may have contributed to the recovery.

### Tuberculous Infections

Three patients with tuberculous pneumonia and six with tuberculous meningitis were treated with full doses of sulfamerazine, which showed no influence on the clinical progress in any of these cases. All died.

### Gonococcal Infections

Satisfactory results were obtained in ten male patients with acute gonococcal urethritis. All recovered and no relapses followed.

### Viral (?) Infections

There were twenty cases in this series which fulfilled the usual criteria for the clinical diagnosis of a probable viral infection. Sulfamerazine was employed in these patients for the following reasons: (1) the presence of an acute infection in which the diagnosis was not adequately substantiated by usual laboratory studies, (2) diagnostically, to determine the response of the disease to the drug, and (3) to prevent, if possible, secondary infection. Fifteen cases of *primary atypical pneumonia* were treated with sulfamerazine and, although the clinical response in this group was not so striking as that observed in the acute bacterial pneumonias, all patients recovered and no complications were seen. Three patients with benign lymphocytic choriomeningitis and two with acute encephalitis were given sulfamerazine with no deaths. In all five of these cases there was striking clinical improvement following the institution of chemotherapy, and it is possible that the drug did influence the course of the disease. Nevertheless, it is difficult to ascertain whether sulfamerazine had any beneficial effect in any of the above cases in which the clinical diagnosis of a viral infection has been made.

### Unspecified Infections

There were eleven patients with bronchopneumonia to whom sulfamerazine was given. A variety of respiratory organisms, other than pneumococci, were isolated from the sputum samples of some of these patients. One died (9 per cent mortality). In eleven cases of acute pyelonephritis, cystitis, or trigonitis, sulfamerazine was used satisfactorily with no deaths. *Colon bacillus*, alone or with other organisms, was cultured from the urine of seven of these patients.

### TOXIC MANIFESTATIONS OF SULFAMERAZINE

A summary of the various toxic manifestations encountered in 400 patients receiving sulfamerazine is given in Table 2.

TABLE 2

INCIDENCE OF TOXIC REACTIONS (400 CASES)

Toxic Reaction	Number of Cases	Per Cent
Gross hematuria	5	1.3
Acute loin pain	4	1.0
Dermatitis	12	3.0
Nausea and vomiting	5	1.3
Leukopenia	9	2.3
Thrombocytopenia	1	0.3
Fever	8	2.0
Psychosis	4	1.0

Forty-eight toxic reactions, attributable to the drug, were noted in thirty-eight patients (9.5 per cent).

### Urinary Tract Complications

As mentioned above, one of the most significant difficulties associated with the use of sulfadiazine is its toxic effect upon the urinary tract, namely hematuria, urinary suppression, and renal colic. These complications are due in part, if not entirely, to the relative insolubility of sulfadiazine, especially its acetyl fraction. In view of the greater solubility of both sulfamerazine and acetylsulfamerazine in urine,<sup>6</sup> as compared with sulfadiazine and acetylsulfadiazine, one might expect to encounter less urinary tract toxicity with the former. Special emphasis was placed on the possible toxic effect of sulfamerazine on the urinary system. A careful check was made as to fluid intake and output. Although alkalis were withheld, this was done for the purpose of giving the drug a more rigid test. Crystalluria, pre-

sumably due to the drug, was observed in approximately 15 per cent of the cases, but we have not considered this finding as being significant unless it was associated with other urinary complications. Likewise, the presence of occasional red blood cells in urine has not been classified as an urinary abnormality due to sulfamerazine because of the frequency with which microscopic hematuria is present with acute infections.

Gross hematuria occurred in five patients (13 per cent), four of whom experienced acute loin pain. In four of this subgroup (aged twenty, fifteen, fifty-five and eighteen years) acute loin pain and gross hematuria developed on the first, fifth, tenth and fourteenth<sup>10</sup> days of treatment following 4, 16, 36 and 77 gm of the drug respectively. The urine in these cases contained many drug crystals as well as innumerable red blood cells. For each patient in this group the urinary output was 1200 cc, or better, for the twenty-four-hour periods preceding, the day of, and following the apparent ureteral blockage. In each instance the drug was stopped immediately and within twenty-four hours after the attack none of the patients offered any symptoms or laboratory evidence of any urinary tract disturbances. Recovery occurred in all of the above cases. The fifth patient,<sup>10</sup> a thirty-year-old male, suffering with subacute bacterial endocarditis, received 14 gm of the drug during the first three days of treatment, with no apparent untoward effect. On the fourth day he was given 25 gm (sulfamerazine sodium) intravenously over a thirty-minute period. A free drug level, taken one hour after the infusion, was 106 mg per 100 cc of serum. The first voided specimen of urine thereafter contained many drug crystals and innumerable red blood cells. With the exception of the finding of occasional red blood cells in the urine throughout the next forty-eight hours and the partial suppression of urinary output for several days, there was no other evidence of renal damage. After five days the patient was again given sulfamerazine by mouth with no further urinary disturbances. The patient finally died and sections of the kidneys were examined and no renal damage was found which could be attributed to the drug.

#### Dermatitis

Skin rashes, developing during sulfamerazine treatment, were encountered in twelve patients (3 per cent). The rash was scar-

littiform in four and maculopapular or morbilliform in the others. These eruptions were observed in only two cases before the seventh day of therapy, in these they appeared on the fourth and fifth days respectively.

### Nausea and Vomiting

In this series there were five patients (13 per cent) in whom nausea and vomiting occurred which we attributed to sulfamerazine. There were cases with vomiting before the drug was given which have been excluded, but in these the vomiting usually ceased after the infection was brought under control. In none of the patients with nausea and vomiting following the administration of sulfamerazine was it necessary to stop chemotherapy because of this toxic effect.

### Blood Disturbances

Nine patients (23 per cent) developed leukopenia (less than 4000 leukocytes per c mm) between the sixth and twelfth day of treatment with sulfamerazine. In two the total white count returned to normal, although the drug was continued, whereas in six the total white count became normal soon after the withdrawal of sulfamerazine. The ninth patient was the one with subacute bacterial endocarditis mentioned previously, who received massive dosage of the drug and developed a thrombocytopenia as well as a leukopenia. A biopsy revealed a generalized hypoplasia of the bone marrow, although within two weeks after the drug was stopped the peripheral blood picture returned to normal.

### Drug Fever

A diagnosis of drug fever was made in eight patients (2 per cent) receiving sulfamerazine. The fever in these cases was encountered between the fifth and fourteenth days of treatment.

### Mental Manifestations

Although it is often difficult to determine whether certain neuropathologic changes are due to the drug or the disease we

have made the diagnosis of drug psychosis in four patients (1 per cent) In two of these, the mental symptoms subsided promptly after the drug was stopped, whereas in the others the mental changes gradually cleared, although the drug was continued

### SUMMARY AND CONCLUSIONS

Sulfamerazine has been used in the treatment of 400 patients with a variety of acute infections From a pharmacologic standpoint, it appears that sulfamerazine is a more satisfactory drug than sulfadiazine in that higher blood levels are attained more rapidly and sustained longer by sulfamerazine than by similar amounts of sulfadiazine Thus, it is possible to maintain a given concentration of drug in the blood with smaller amounts of sulfamerazine than sulfadiazine Likewise, this feature of sulfamerazine may prove it to be superior to sulfadiazine as a *prophylactic agent* Furthermore, the rapid absorption obtained with sulfamerazine frequently makes the parenteral use of the drug unnecessary

The therapeutic results obtained with sulfamerazine in the cases of pneumococcal and meningococcal infections are comparable in every respect with the results obtained by us with sulfadiazine In the other conditions in which sulfamerazine was employed the limited number of cases involved prevents a definite comparison, although it appears that sulfamerazine is as effective as sulfadiazine in the various infections in which it was used<sup>19</sup>

In general, the toxicity of sulfamerazine is low and is no greater than that of sulfadiazine Gross hematuria, occurring in four patients receiving routine sulfamerazine treatment and in one given massive intravenous therapy, indicates that the drug may cause urinary tract disturbances. It is possible that some of these urinary tract complications might have been prevented or minimized had we employed medication with alkali<sup>20, 21</sup> At least, the fact that urinary complications occurred makes the routine use of alkalis advisable

It appears that sulfamerazine, by virtue of its pharmacologic behavior, therapeutic efficacy and low toxicity, offers definite advantages over sulfadiazine and is worthy of extensive clinical trial

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# THE DIFFERENTIAL DIAGNOSIS OF ACUTE ABDOMINAL CONDITIONS\*

W. OSLER ABBOTT M.D., F.A.C.P.†

It is a natural instinct with all of us on seeing an acutely ill patient to leap for a diagnosis that no time may be lost in beginning treatment. Under such circumstances it would be absurd to set about the taking of a long formal history, for in many instances the patient himself cannot give it and the friend who brings him does not know it. Nevertheless, without system of some sort we will too often find ourselves in that embarrassing position of having the abdomen open but no lesion discoverable to account for the patient's condition. The problem therefore boils down to the question of the essential minimum. What question, what studies will yield the maximal diagnostic evidence with a minimum of wasted time and effort? What are the key points that identify the pathological process and the organ involved by it?

## EXAMINATION OF THE PATIENT

### I. A Consideration of Symptoms

The primary symptoms presented by acute abdominal conditions are (a) pain of four primary types, (b) distention or the evacuation of contents by mouth, bowel, bladder, or vagina and (c) systemic symptoms such as fever, prostration and dyspnea.

(a) ACUTE ABDOMINAL PAIN—Acute abdominal pain is ordinarily caused (1) by ischemia of muscle tissue, (2) by occlusion of a hollow viscus, (3) by serosal irritation, or (4) by stimulation of peripheral nerves. Since different organs and different disorders yield different types of pain and since the pains may commonly be distinguished on the basis of intensity, duration, location and radiation, one from another, their identification is important.

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\* From the Medical Clinic, Hospital of the University of Pennsylvania.

† Assistant Professor of Medicine, School of Medicine, University of Pennsylvania. Ward Physician, Hospital of the University of Pennsylvania.



*Ischemic pain* is typified in the body by the pain of a coronary occlusion. It is of great intensity, continuous in duration and fixed in position. In the abdomen such pain results from the cutting off of the blood supply to muscle but not to glandular or parenchymal tissue. Strangulation of the intestine by a hernia, a volvulus or an intussusception produces it most frequently but occlusion of a branch of the mesenteric blood supply by a thrombus or embolus must be considered when conditions favor the occurrence of such accidents. In my experience, mesenteric occlusions have most commonly happened a few days after a large coronary occlusion that has led in turn to the formation of a friable mural thrombus in the heart chamber.

*Colic* is the pain originating from contractions occurring in an occluded hollow viscus. It is intense while it lasts but comes and goes recurrently. Its location is ill defined in organs with a mesentery such as the small intestine, but is well defined in those organs having retroperitoneal surfaces such as the ureters or the flexures of the colon. A colicky pain therefore suggests an occlusion of the biliary tracts, the ureters or the alimentary canal.

*Serosal irritation* causes persistent pain localized, if the parietal peritoneum is involved, and exaggerated by movement of one surface upon another as in pleurisy. Therefore, the pain of a perisplenic inflammation is exaggerated by respiration. Infections above or below the liver are commonly caused by the localization of pus resulting from a ruptured peptic ulcer or an empyema of the gallbladder. In either case the inflammation is severe enough to stop diaphragmatic movement on that side. An infarct of the spleen, however, gives a pain closely simulating a left basal pleurisy. The strapping that would relieve the pleurisy accentuates the splenic pain, however, by increasing the diaphragmatic excursion. Acute abdominal distress from serosal irritation is generally accompanied by fever.

*Nerve pain* if limited to the abdominal wall is usually of a constant grade of intensity punctuated by severe lancinating exacerbations that radiate along the distribution of the nerve involved. The patient often refers to it as a "burning" pain. Typical is herpes zoster. When the pain precedes the eruption it is most important to determine that it is in the abdominal

wall and not originating in the underlying viscera. If a supine patient tightens the abdominal wall by lifting his head and his feet from the table the tenderness of a visceral lesion to palpation will be diminished by the protection of the tight muscle, but the tenderness of a neurogenic lesion will remain unabated. Disorders that give not only peripheral root pain but also disturbances of visceral motility, such for example as *tabes dorsalis*, are far more difficult to distinguish from visceral pain on abdominal examination alone. Unless a complete physical examination has revealed the pupillary and reflex changes of neural syphilis, one might easily be led into the error of operating. It is rare but not impossible that other neurological lesions be mistaken for acute visceral disorders. I have seen a man's appendix removed because the first hyperesthesia of oncoming poliomyelitis chanced to be in the right lower quadrant of his abdomen.

When the acuteness of a man's illness limits the taking of a history, the value of exact information on the intensity, quality, duration, location and radiation of the pain cannot be exaggerated.

(b) THE PROBLEM OF EVACUATION.—This problem ranks next to that of pain in acute conditions. Is there a history of distention, of obstructed flow from the bowel, the biliary tract, the bladder or the vagina, or is there a reverse flow in the digestive tract with vomiting? Obviously the distention will be related to the volume evacuated by the viscus. Obstruction of the common duct may render the liver and occasionally even the gall-bladder palpable. Obstruction of the intestinal tract may grossly distend the whole abdomen. So much is obvious, the confusions arise when the obstruction is partial. A story of frequent small micturitions may suggest not only a small irritated bladder but a distended, almost obstructed organ. The story of an effectual enema or a bowel movement is no denial of an intestinal obstruction, for the bowel distal to the lesion may contain considerable amounts of feces. The character of the discharge whether mixed with fresh blood from a low lesion or with digested blood from a high lesion, the appearance of foreign bodies, kidney stones in the urine, gallstone in feces, the presence or absence of bile in urine or vomitus—all are points that narrow the differential diagnosis.

(c) THE SYSTEMIC RESPONSES —The systemic symptoms are the third major consideration in the history. The presence of tachycardia, prostration and shock may be important differentials. Their significance will be considered under separate headings below.

## 2 Physical Signs

The physical signs presented by the patient may be local and correlated with the lesion itself, or generalized.

(a) LOCAL SIGNS —The local signs of importance in examining a patient with an acute abdominal condition are of course tenderness, whether generalized or localized, involuntary rigidity, and the presence or absence of a mass. If a mass is felt, its size, shape and the location in the abdomen give an inkling as to its origin. Movable masses migrate to the midline as they enlarge in the lower abdomen and from the midline in the upper abdomen. Nevertheless, because the anteroposterior diameter of the abdominal cavity is least in the midline above the promontory of the sacrum, that part of the mass extending toward the midline may be more easily felt.

The two least used of the valuable signs, however, are inspection of the abdomen for visible peristalsis, particularly that of gastric or colonic origin, and auscultation of peristalsis. The latter requires much study if full value is to be derived from it, but if given attention, it will yield most valuable information.

(b) GENERALIZED SIGNS —The generalized signs are not only the temperature, pulse and blood pressure, which give the first indication of the systemic reaction of the patient to his illness, but the rapidity with which metabolic imbalances follow abdominal catastrophes necessitate the observance of other indicators.

*Dehydration* in a vomiting patient may be judged by the turgor of the subcutaneous tissues. The great fluid reserve of the body is the extracellular interstitial fluid. As that is depleted the elasticity of the tissue beneath the skin is lost and a fold pinched up on the forearm fails to flatten out promptly, as though the skin were turned to putty. If dehydration increases the intravascular fluid reservoir diminishes. *Decreased blood volume* is early suggested by a failure of the veins over the back

of the hand to fill promptly and the nail beds become cyanotic from capillary stasis. As this is the step preliminary to *shock*, it is of vital importance to recognize it. When shock has become established the characteristic rapid "thready" pulse appears, the "thready" character being due to the low blood pressure.

Another metabolic change suggested by physical signs is related to the acid-base balance. If vomiting is causing loss primarily of gastric acid, the ensuing alkalosis will be suggested by Chvostek's signs—the twitch of the face caused by striking the region of the seventh nerve in front of the ear or by Trousseau's sign—the carpopedal spasm that results when the blood pressure cuff is kept for a few minutes on the arm.

### 3 Basic Laboratory Data

The basic laboratory data in these cases should include the *white blood cell count* for the identification of infection, the *hemoglobin* as an estimate of hemorrhage and sometimes of hemoconcentration, the determination of the *urine specific gravity*, *urine sugar* and *urine blood cells* whether red or white. If the patient is vomiting, a specimen of blood should be analyzed for chlorides, protein and carbon dioxide. A *roentgenogram* of the whole abdomen is advisable with the patient supine and if possible with him erect. The ruling in or out of (a) the presence of air under the diaphragm which often occurs when a peptic ulcer has perforated, (b) the ladder pattern of an obstructed intestine, (c) fluid in a distended inactive intestinal loop, (d) loss of psoas shadows suggesting retroperitoneal disease, and (e) calcification or displacement of organs is all-important. In short, the scout film is an invaluable diagnostic aid.

### CONDITIONS ARISING FROM DIFFERENT ORGANS

The preliminary consideration of the symptoms will often identify not only the nature of the process but by its character and location may show from which organ it originates. Let us now consider the acute catastrophes most likely to arise from each organ. It is by acquiring the habit of such an orderly process of mind that we are saved from jumping to the most obvious rather than to the most probable diagnosis.

## 1 Peritoneal Cavity

The peritoneal cavity rarely becomes involved in acute conditions with antecedent localized symptoms. Pneumococcal peritonitis in girl children is an exception. In adults, the rupture of an *ectopic pregnancy* may infrequently fail to give localized symptoms before the peritoneal cavity fills with blood. I have twice seen the spontaneous rupture of *mesenteric vessels* into the peritoneal cavity in old arteriosclerotic men. When rapid diffuse hemorrhage into the peritoneal cavity does occur, generalized tenderness of the abdomen without rigidity and often with accelerated peristalsis is apt to be superimposed upon the symptoms of severe hemorrhage from any cause.

## 2 Gastro-intestinal Tract

The gastro-intestinal tract is the site of *strangulations*, *obstructions*, perforations, hemorrhages and infections producing acute conditions.

**STRANGULATIONS**—Strangulation gives rise to severe unremitting pain, but, because it is usually associated with obstruction of the intestine, waves of colic cause recurrent intense exacerbations. *Hernias* into the inguinal, femoral or umbilical ring cause the great majority of strangulations. These are commonly palpable. Second in frequency are the internal hernias caused by bands and adhesions and peritoneal pockets. They are rarely palpable. Far less frequent, save in children, are *intussusceptions*. *Volvulus* is the least frequent of the major causes.

The distinction between intestinal strangulations and simple obstruction is of the utmost importance since strangulations require immediate surgery while simple obstructions, if severe, may need days of preparation before an operation may safely be performed. The pain of a simple obstruction ceases almost completely between waves of colic while that of a strangulation is maintained at a high level of intensity. The tenderness of a simple obstruction is generalized and that of a strangulation is localized. The colic of simple obstruction is stopped by 10 mg of morphine sulfate subcutaneously. The pain of strangulation is rarely stopped by such a dose. A simple obstruction may take several days to kill the patient. The symptoms of a strangulation may reach a lethal intensity in twenty-four to thirty-six hours.

**OBSTRUCTION OF THE INTESTINE.**—Obstruction not only yields the colicky pain described but evidence of interruption of the flow, dimming back of the contents and reversal of the current

The flow of feces is cut off from its source. A bowel movement may occur or one enema may be effectual depending on how much feces lies distal to the blockage, but this should not hide the fact that an obstruction has occurred. Distention begins simultaneously in the region above the obstruction and in the stomach, the intervening length of intestine becoming distended as time goes on. Peristalsis is first increased in frequency and intensity, then in pitch, then the frequency diminishes and finally before peristalsis disappears it is infrequent, but has the high metallic tone of a plucked banjo string. Gradually all sounds lose intensity until a "silent belly" results. In this condition, rolling the patient on his side produces sounds like liquor bubbling out of a demijohn.

Fullness, belching, nausea, vomiting and fecal vomiting appear in rapid succession from the onset.

This picture is usually clear-cut if the occlusion is complete, and of mechanical origin. The so-called paralytic obstruction or ileus should be included here, however, because intestinal obstruction is a "functional" diagnosis. Anything that prevents the passage of content from mouth to anus leads to death whether the cause is mechanical, "paralytic," "inflammatory," or otherwise. Any condition that stops intestinal flow is therefore significant in diagnosing obstruction. The important point is neither to mistake a functional obstruction for one of mechanical origin, or vice versa, since the therapy is wholly dissimilar, nor to focus attention on the obstructive syndrome and fail to note the primary cause. Patients with renal stones, with Addison's disease and with azotemia have been operated on for intestinal obstruction. It is true the gut was obstructed but the obstruction was wholly functional in character.

Fever and leukocytosis appear early in strangulated obstructions but late in simple obstructions. Laboratory studies show (a) concentration of the blood, (b) hypochloremia and (c) hypoproteinemia. If the obstruction chances to be at or near the pylorus, alkalosis is indicated by a high plasma carbon dioxide.

The x-ray is very valuable in showing the distribution of gas in the intestine which not only confirms the diagnosis but occasionally helps to localize the lesion. Intestinal intubation, which is indicated in most nonstrangulated cases, makes possible the injection and subsequent withdrawal of an opaque medium for roentgenograms. By this means the surgeon operates with a clear idea of what he will have to do.

**PERFORATIONS**—Perforations of the digestive tract occur from different lesions in the following order of frequency: *appendicitis*, *duodenal ulcers*, *gastric ulcers*, *colon carcinomas*, *colon diverticula* and *Meckel's diverticulum*. The diagnosis is often suggested by the antecedent symptoms, but when a perforation occurs suddenly it produces the most intense form of serosal irritation pain. This is particularly true of the gastric and duodenal lesions and in any case the pain is proportional not only to the irritating quality of the juice released into the peritoneal cavity but to its volume. Thus a gastric ulcer perforating when the stomach contains 300 to 400 cc of highly acid liquid produces far more abrupt and intense symptoms than a colonic diverticulum leaking out a few drops of feces. Tenderness occurs promptly and is localized in proportion to the volume of "spill" and to the drainage gutters of the belly. Half a pint of gastric contents may finally collect in the rectovesical pouch and tenderness may then involve the whole abdomen. Boardlike rigidity results, accompanied by the systemic indications of shock. The bacteriostatic action of acid gastric juice renders the factor of infection less than in the case of a colonic perforation. The latter begins in a less fulminating manner, but the symptoms increase in severity as the peritonitis spreads.

Whenever there has been a perforation, fever and leukocytosis may be expected, but one of the most useful findings, if present, is the x-ray demonstration of gas under the diaphragm in a film taken with the patient standing.

**SEVERE HEMORRHAGE**—Severe hemorrhage from the digestive tract occurs in a descending order of frequency from *duodenal ulcers*, *gastric ulcers*, *gastric cancers*, *esophageal varices*, *Meckel's diverticulum*, and, finally, from *benign tumors* of the intestinal wall. While right-sided colonic cancers often manifest themselves first by the production of anemia, it is rare

for one to gush blood as the above named lesions do. It is even doubtful whether gastric cancer deserves the position given it, for while hematemesis is often the first symptom, it is rarely a sudden bleeding capable of prostrating the patient.

Duodenal ulcers stand so far in the lead that any patient passing tarry stools and vomiting blood may be assumed to have a duodenal ulcer till proved otherwise. Antecedent evidence of hepatic cirrhosis will suggest esophageal varices. Age, weight loss and a supraclavicular lymph node on the left will suggest a gastric cancer, but the problem becomes difficult when tarry stools are passed by a young man who does not vomit blood or who, on gastric lavage, has no blood in his stomach. The chances are still in favor of its being a duodenal ulcer but the possibility of a Meckel's diverticulum must be seriously considered. If the bloody stools are reddish rather than tarry, it may be safer to give the patient a swallow of barium and fluoroscope him (without palpation) since a Meckel's diverticulum should be operated on and a bleeding duodenal ulcer should not.

**INFECTIONS**—Infections of the digestive tract deserve a word also, for while acute dysenteries and cholera are apt to appear in epidemic form if at all, sporadic fulminating "food poisoning" occurs not infrequently. This is commonly caused by an overwhelming dose of staphylococci. A baker coughs into a batch of cream puff filling and puts it in a warm place. Some time later he fills a "shell" with what by then may be a massive culture of the organism. The result is a widespread necrosis of the intestinal mucosa. One sporadic case of this sort may be a real diagnostic problem.

### 3 Biliary Tract

Biliary tract lesions that are acute are most commonly caused by (*a*) stones in the cystic duct (without jaundice), (*b*) stones in the common duct (with jaundice) and (*c*) empyema of the gallbladder with the fever, leukocytosis, local pain and tenderness that would characterize any abscess.

Acute disorders of the gallbladder and bile ducts affect women more often than men, they rarely occur before thirty years of age and are not common before forty, they are associated with a sense of flatulence and often intense belching and nausea, but perhaps most characteristic is the reference of the



pain. As a rule this centers over the right hypochondrium, radiating either "through" or "around" to the angle of the right scapula. Much has been said of right shoulder pain in biliary tract disease, and it is true that occasionally a reference to the right trapezius ridge does occur but this is less notable for its frequency than for its interest when it occurs. The frequency with which the symptoms of gallbladder disease suggests those of an active ulcer leads me to emphasize one other small point. An ulcer patient presses on the sore spot for relief. A gallbladder patient may find even the contact of clothes intolerable. Finally, however, it is jaundice that stands out as of chief importance. Gallbladder colic is not associated with jaundice, for the common duct is clear. If jaundice occurs the obstruction is between the liver and the intestine, and carries with it the threat of serious hepatic damage.

#### 4. Urinary Tract

Acute urinary tract conditions are less likely to be mistaken for other things because of the radiation of pain to the groin and often to the testicles in men, and because of the blood in the urine though sometimes in microscopic amounts. In women, however, the reference of pain may at times confuse the condition with diseases of the fallopian tubes. It is also worth noting that reflex digestive symptoms promptly set in when a stone enters a ureter, so that occasionally patients with ureteral calculi are mistakenly admitted for intestinal obstruction.

#### 5. Female Genitalia

Acute disorder of the female genitalia are rarely mistaken for other conditions, because of their antecedent symptoms. Occasionally a girl who does not know that she is pregnant suffers a spontaneous rupture of an ectopic pregnancy or in older women a subserosal myoma or ovarian cyst becomes twisted on its pedicle with strangulation. On the whole, however, the nature of the acute conditions is usually fairly clear.

#### 6. Pancreas

The pancreas is an infrequent source of acute illness, but when acute hemorrhagic pancreatitis occurs, its diagnosis is by no means easy. The severe shocking pain going through to the back and the unmistakable evidence that a major catastrophe

has overtaken the patient cannot be missed, but the perforation of a gastric ulcer into the lesser peritoneal cavity or an acute cholecystitis may be strongly simulated. This is especially true when one considers the small but important percentage of pancreatitis cases which simultaneously present a gallstone in the common duct. Were operative intervention helpful in all these conditions, an exact diagnosis would be of little importance, but surgery offers little to the acute pancreatitis patient, and there are many who would avoid immediate operation on these patients if they could be selected with certainty.

One special test is almost diagnostic here but is so dependent for its accuracy upon the experience of the technician that few hospitals hold it available. Indeed few hospitals see enough acute pancreatitis to allow the laboratory to gain any experience, but when it can be done the blood amylase determination is diagnostic. For the few hours succeeding the onset of an attack the amylase content of the blood is very high. Later it falls without alleviation of the condition and means nothing. The test therefore is of most value at the stage of the disease when information is most needed.

## 7 Nervous System

Neurological lesions have already been mentioned in the discussion of pain but should be re-emphasized, since they are rare enough to be easily overlooked. The abdominal pain is in the belly wall rather than in the viscera in herpes zoster, intercostal neuralgia and the girdle pains of tabes, but the extrinsic nerves of the viscera may carry in from parts remote from the peritoneal cavity, impulses that disrupt visceral function. After brain operations, including those on the pituitary gland, acute perforating or hemorrhagic ulcers of the stomach and duodenum occasionally form. Attacks of migraine may occur simulating cholecystitis. Epilepsy in rare instances affects the digestive tract alone with such violent colic as to almost reproduce the intussusception appearing in the small intestine of a monkey during appropriate cortical stimulation.

## NONABDOMINAL CONDITIONS

Finally, there are those conditions manifesting themselves in acute abdominal symptoms that are of systemic rather than local origin.

## Metabolic Diseases

Amongst the metabolic diseases we must remember that *diabetic acidosis* in the young patient is often accompanied by right lower quadrant pain, nausea, leukocytosis and fever. The smell of acetone on the breath of such a patient may save an operation that is not only needless but under the circumstances harmful.

Acute *porphyria* is rare enough to pass unrecognized particularly if it is the type without "port-wine" urine. The intensity of the colic and absence of diarrhea may suggest intestinal obstruction, but the subnormal mentality usually points to porphyria and the diagnosis may be clinched by acidifying the urine and seeing it fluoresce red under an ultraviolet lamp.

Crises of *Addison's disease* with rapidly developing distention have been mistaken for intestinal obstruction, and where the pigmentation has been overlooked, the low blood pressure has been thought to be a part of shock.

## Hematologic and Cardiovascular Disorders

A hematological condition falling within this field is *sickle cell anemia*. The abdominal pains incident to this disorder have led also to needless appendectomies, though here again if one but suspects the possibility, a distinguishing point is ready at hand. Since the attack of sickle cell anemia is an acute hemolytic process the reticulocyte count is characteristically elevated.

Among cardiovascular disorders that are confused with abdominal disease, *myocardial infarction* has received proper emphasis. There are cases of coronary artery occlusion in which the pain is referred to the epigastrium but the electrocardiogram, particularly with chest leads, is now so accurate and so accessible that the diagnosis should not be long in doubt.

## Intoxications

Finally, intoxications must not be overlooked. These may be accidental and range from *lead poisoning* to "*black widow*" spider bite. To think of the possibility is generally to discover the diagnosis. There may also be criminal poisonings. The *arsenic* "insurance murders" of a few years ago were promptly recognized as such. And in conclusion, one must consider the effect of "*intoxication*" in the ordinary sense. I re

member a lumberman admitted with what seemed clearly a perforating gastric ulcer. Two hours later the resident was sure the patient had a stone in the cystic duct. Next day he passed bright blood by bowel and had an excruciating pain over the cecum. That night he was heard screaming in the toilet and wedged in his anal sphincter was a triangular piece of tin roughly 2 cm on each side. When confronted with it he denied any recollection of having swallowed it, but admitted that the night before the first attack he had celebrated with some friends until morning.

## TROPICAL DISEASES OF CONCERN TO THE HOME FRONT

WILLIAM HARVEY PERKINS, M.D., Sc.D.\*

YEARS of intelligent planning by the health services of the United States has resulted in the development of formidable defenses against importation of many tropical and exotic diseases. Vigilance within the continental boundaries of this country has eliminated or brought under practical control many diseases that formerly existed here but still occur in other countries. Awareness of the potential dangers from without on the part of our general medical profession has not been developed equally with that of the few who know on how narrow a margin we operate against the growth and spread of the so-called exotic diseases that menace us.

The home front is in danger from many diseases, largely of bacterial or parasitic origin, that can and might increase here unless the barriers remain effective or new ones are built against new threats.

An obligation is assumed by every practitioner to notify the health authorities of certain diseases coming under his observation. State and municipal health departments, the United States Public Health Service and the medical services of our armed forces depend largely for their knowledge of diseases existing among us on the accuracy of information supplied them by the civilian doctors. The completeness of this information rests largely therefore on the diagnostic acumen of the private practitioners and the degree to which they give notice of the reportable diseases among their patients.

Freedom from the great epidemics of former times and the little opportunity given to the doctors in this country to know about them through study or experience has resulted in an almost contemptuous attitude toward them. World War II has

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\* Dean and Professor of Preventive Medicine, Jefferson Medical College, Attending Physician, Jefferson Medical College Hospital

jolted us into consciousness of the fact that the epidemics and plagues of other countries are today approaching perilously near our own shores. There is already evidence that some have entered our borders and are no longer only theoretical invaders. Straggling remnants of the great plagues of Europe and the Orient in certain areas of this country are evidence of their presence here in times past, that they cannot resurge in serious proportions is not assured us.

The war is a medical emergency in the United States, not only because of war casualties and the problems of ordinary medical care of millions of our citizens now in service at home and abroad but because the conditions of war have disturbed the balances of control that have limited the prevalence and spread of the little-known and long-feared world plagues.

A realistic study of the tropical diseases reveals the seriousness of the present situation. In general we are faced with the possibility that three groups of tropical diseases can and may assume serious proportions within this country. These groups are (I) those already present to some degree among certain groups of our population, (II) those formerly prevalent here even in epidemic proportions but that have not been recognized or reported in the United States for a number of years or decades, (III) diseases of endemic or epidemic occurrence in other countries that have never been recognized within our continental boundaries.

Familiarity with the tropical diseases has become an essential obligation of every practitioner in this country, he must know them by name, anticipate their occurrence, be informed on how to recognize them and know at least something of their care, treatment and control.

## I TROPICAL DISEASES CURRENTLY PRESENT IN THE UNITED STATES

### Malaria

The story of malaria is the story of the *Anopheles* mosquito. Within the limits of the factors that determine the survival of the parasite and the insect host, malaria is possible anywhere that this mosquito exists. Within the United States, its geographic distribution is widespread. Malaria in one form or another has always been present in this country and has been

a disease of great medical and economic importance. The physicians of the past generation were greatly concerned with it in areas in which it is now nonexistent or appears so rarely that it is considered of little significance. The typho-malaria of the earlier years of this country's medical history is evidence of the confusion and difficulty in differentiating two diseases of heavy prevalence during those times.

The changing picture in the prevalence rate of malaria in the various states of this Union can be ascribed with little hesitation to the influence of two factors: (1) antimosquito campaigns, whether directed primarily against the malaria-carrying mosquito or against mosquitoes generally as nuisances, and (2) general socio-economic improvements that have changed our environment and living conditions in such a manner as to militate against the factors favorable to the persistence of malaria.

*Control Measures*—Antimalarial measures against all factors responsible for the propagation of the mosquito and the spread of the plasmodium is the only effective approach to the control of this disease. Recognition, diagnosis and treatment of cases of malaria are not to be minimized but they cannot alone be effective against a disseminating mechanism as widespread as mosquito transmission. The part played by the physician in the sterilization of all malaria patients under his care removes a certain part of the hazard but cannot be counted upon for eradication of the disease from the population.

In a peacetime American community mosquito control is reasonably accomplished. It involves the expenditure of considerable sums of money and much may be wasted in ineffectual measures unless those who accept responsibility for mosquito control are well informed on the details. Specifically, this means a knowledge of the species of mosquitoes to be eliminated, including their breeding habits and the special geographic, meteorologic and social factors involved, as well as an understanding of the changes in the environmental conditions most likely to be detrimental to the mosquito population.

Thus, where time is of little concern, measures such as drainage, diversion of streams, land clearing, oiling and the spreading of larvacides are the most effectual far-reaching procedures to be adopted.

When the menace of malaria in a community is imminent and serious the immediate control measures must become centrifugal,

ie, they must begin with the individual and progress outward through the community. Such measures will be early diagnosis and adequate care of malaria patients, suppressive (prophylactic) treatment of those exposed, mosquito bars and nets for individuals, screening of windows and homes, and finally, household and community attacks on domestic and neighborhood larva-breeding places such as cisterns, pots, drains, and other water-containers, and out-door pools, ponds, ditches, low-lying areas and other natural or artificial collections of water.

*Prophylaxis*—Malarial infection cannot be prevented in the individual by antiparasitic drugs. The prophylactic use of quinine cannot prevent infection by the invasive stage of the protozoa but it can destroy plasmodia in the blood at other points in their human cycle and thus act as an inhibitor of the full clinical manifestations of the disease. This is expressed in the new belief that quinine prophylaxis is suppressive treatment rather than preventive.

*Treatment*—Effective treatment of malaria is best obtained at this writing by the combined use of quinine, atabrine and/or plasmochin. Each of these drugs has specific effects on the developmental forms of plasmodia. In general, quinine and atabrine destroy the schizogonic forms of benign, quartan and aestivo-autumnal malaria parasites and the sexual forms of tertian malaria but are less effective against the gametocytes of quartan and aestivo-autumnal plasmodia. Plasmochin on the other hand produces no effectual results against any of the asexual forms of any types but destroys the sexual forms of all types. None of the three drugs mentioned will destroy sporozoites. Because of this fact infection can occur even in the presence of these substances in the blood and it is for this reason that no known drug is considered to be a true preventive.

#### RECOMMENDED TREATMENT OF MALARIA (COMBINED USE OF QUININE, ATABRINE AND PLASMOCHIN)<sup>1</sup>

1. Quinine sulfate, 10 grains (0.64 gm) three times daily after meals for two or three days, or until pyrexia is controlled. Then give

<sup>1</sup> Acknowledgment is made of the liberal use of the recommendations of the Subcommittee on Tropical Diseases of the National Research Council as presented in the notes published by the United States Naval Medical School, October 1942, and Circular Letter No. 33 from the Office of the Surgeon General, War Department, February 2, 1943.



2 Atabrine,  $1\frac{1}{2}$  grains (0.1 gm) three times daily after meals for five days. Then after two days without antimalarial medication, give

3 Plasmochin,  $\frac{3}{20}$  grain (0.01 gm) three times daily after meals for five days, except for the debilitated patient, who should receive only two doses daily. Discontinue if toxic symptoms occur.

*Never give atabrine and plasmochin concurrently*

When quinine is not available use atabrine for seven days and then after two days' interval use plasmochin.

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In comatose patients or those with vomiting, who are unable to take medicine by mouth, give quinine dihydrochloride intravenously as 5 to 10 grains (0.3–0.6 gm) to 100 to 200 cc of sterile normal saline solution. Give this amount over a period of about thirty minutes. Repeat every eight hours until the patient can take quinine by mouth.

Atabrine dihydrochloride may be substituted for quinine in these cases but is to be given intramuscularly in alternate buttocks in doses of 0.2 gm. Repeat at eight-hour intervals.

### Amebiasis

American plumbing has saved this country from a serious, widespread incidence of amebic dysentery. Surveys indicate that something like 10 per cent of the population of the United States harbor *Endamoeba histolytica*, the causative protozoan parasite. That this has not resulted in more outbreaks of severe epidemics is a triumph of sanitary engineering and a tribute to the high-level food habits of the population.

*Endamoeba histolytica* always produces lesions in its human host, but for unaccountable reasons seldom results in this country in the serious dysenteric form of the disease. How much disability results from this infection is not known. Many of the undiagnosed intestinal disorders that swell the sickness rates of industrial reports on absenteeism may be of this origin. Failure to recognize the cause is due largely to unawareness of medical practitioners generally that the menace exists in any important proportions.

Granting that there will be no let-down in our general sani-

tary standards, the burden of the control of amebiasis and amebic dysentery must rest almost solely on recognition of the disease.

The diagnosis of amebiasis is made by finding the parasite in the stools. The techniques of fecal examination are simple but the recognition of the pathogenic amebae is a matter for experts. Until physicians recognize their limitations and call upon those qualified to diagnose the vegetative and cystic stages of amebae in stool samples, they will continue to be overlooked and misdiagnosed, amebiasis will remain unrecognized and the disease will continue at its too-high endemic rate.

*Treatment*—Dysentery cases due to this organism, whether acute or chronic are best treated by intramuscular injections of emetine hydrochloride. It is administered in  $\frac{1}{2}$ -gr (0.03-gm) doses twice a day for four to six days. Carbarsone in doses of 4 grains (0.25 gm) three times a day by mouth should be given concurrently with emetine but should be continued for one week. Following the week on carbarsone the patient should be placed on vioform (4 grains) or diodoquin (9 grains), by mouth, three times daily, for another week. Ineffectual treatment from such a course usually requires supplemental rectal instillations of carbarsone or chiniofon, the former as a retention enema at night, made up of 30 grains (2 gm) of carbarsone in 200 cc of a 2 per cent sodium bicarbonate solution and the latter as 60 grains (4 gm) of chiniofon in 200 cc of sterile water instilled per rectum. Each of these instillations should be preceded by a cleansing enema.

### Bacillary Dysentery

The devastating prison and camp dysentery of former days has become a thing of the past in this country. Sporadic outbreaks of bacillary dysentery still occur when the commonly accepted food precautions have been permitted to lapse or, in some instances, where unforeseeable mass infection of food has occurred. The *Shigella* organism responsible for this disease must be carried directly or indirectly from the intestinal canal of a person harboring it to a susceptible individual. The chain of events in this transmission may be as direct as immediate contamination of fingers, food, or drinks by alvine discharges or as remote as contamination from dirty utensils and containers.

or by flies. For these reasons the propagation of *Shigella dysenteriae* depends on unhygienic habits of individuals, faulty food processing, the preparation and cooking of food under unsanitary conditions, and exposure of food and drinks (particularly milk) to conditions of temperature and moisture favorable to its growth.

*Control Measures*—It is assumed that military installations will continue their efficient policing of kitchens, mess halls and food-handling personnel that has been so effective in eradicating camp dysentery from our armed forces. The same degree of precaution should be taken by medical municipal and other authorities over all concerned with the preparation and serving of food and foodstuffs in public eating places. Proper sewage disposal under all conditions must continue.

In spite of all precautions, cases of bacillary dysentery will continue to appear. The circumstances under which they occur may often be difficult to determine, but if they are duly reported by physicians and the responsible health authorities are alert and active in their follow-up of the outbreak there can be no real danger of widespread dissemination of this disease. With little question, the continuance of any significant number of cases of bacillary dysentery in a community is an indictment of the medical profession, official and otherwise.

The principal duty of the practitioner is the diagnosis and treatment of his cases and, recognizing its nature, his participation in the control of the disease by placing the known cases on sanitary precautions.

*Treatment*—For immediate treatment sulfaguanidine is the most effective medication. Given in doses of 3.5 gm (52½ grains) every four hours, by mouth, day and night, sulfaguanidine will reduce the daily number of stools to five or less in a very few days. When it has done so, the drug is continued at the same dose at eight-hour intervals until the stools have been normal for four days. Failure of the case to respond after a week of such therapy is an indication to discontinue the use of this drug. Sulfthiazole or sulfadiazine in doses of 4 gm. (60 grains) every four hours, by mouth, may be substituted for sulfaguanidine if necessary.

The loss of fluids should always be replaced by an adequate intake, either by mouth or intravenously.

The stools and all clothing, bed-clothes and dishes used by dysentery patients should be sterilized by heat or chemicals

### Dengue

The littoral of the Gulf States is an area of repeated occurrence of dengue and from Florida to Texas outbreaks of the disease have occurred in the last two decades that involved hundreds of thousands of the population

From the point of view of mortality, dengue is the least important of all epidemic diseases of the tropics, for it is not fatal. Viewed from the temporary disability produced by an attack, an epidemic of dengue is capable of producing widespread invalidism and incapacity for work not only during the attack but throughout a very uncertain period of convalescence.

Dengue is a virus disease, transmitted by the mosquito *Aedes aegypti*, and in this country probably also by *Aedes taeniorhynchus*. The patient is infective for the mosquito from any time between the few hours before the onset and the third or fourth day of the disease. The mosquito becomes infective for man about ten to fourteen days later.

The conditions for the accentuation of the disease to epidemic proportions are those that favor the increase in the mosquito population, enhancement of their chances of survival and their access to man, and the relative number of infected and susceptible individuals in the community.

Such a concourse of events has happened occasionally in the Gulf States and occurs repeatedly throughout the tropics.

The return of thousands of our military personnel from dengue-infested countries, some of whom may carry the active virus in the seven to nine days of the incubation period, will augment at least one factor favorable to an increased incidence here. Whether or not this can result in epidemic proportions cannot be predicted. It is certain, however, that no soldier returning to this country from endemic dengue areas should be permitted freedom among the general population until he has been under observation for the period of incubation and under conditions where the favorable mosquito carrier can not have access to him.

There is no specific preventive, treatment, or diagnostic test for dengue. The important problems connected with it are

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There is no specific preventive, treatment, or diagnostic test for dengue. The important problems connected with it are

therefore those of mosquito control and the diagnosis of the case. The former is adequately dealt with elsewhere.

*Differential Diagnosis*—Differential diagnosis is largely a matter of eliminating those conditions which it may simulate: influenza, malaria, yellow fever, relapsing fever, smallpox and the so-called denguelike fevers. Dengue has not the acute catarrhal symptoms of influenza, and its postorbital pains and pain near all large and small joints are far more intense than the generalized aching of influenza. The differentiation between yellow fever and dengue will ordinarily be made by the appearance of jaundice and severe albuminuria in yellow fever and the macular, peripherally-beginning eruption around the fourth day of dengue. In retrospect, the saddle-back temperature curve and the slow pulse may appear quite similar in both diseases. The absence of breakbone pains and time will differentiate the course of relapsing fever from dengue, while the leukocytosis and rash of smallpox will ultimately reveal the true nature of this disease. There is no practical way to differentiate the five-, six-, and seven-day denguelike fevers of the tropics from dengue until after the event. Even then, the ultimate course of the disease may make it possible for only a shrewd guess that it was not typical dengue.

### Leprosy

This is a disease of practically all countries and deserves special consideration under Tropical Diseases only because of its present high incidence in tropical areas.

In the United States cases still continue to appear sporadically in the population. While many of our segregated cases at Carville, Louisiana, are importations from other countries there are some that undoubtedly have contracted and developed their infection within this country. How or in what manner their infection was acquired is entirely unknown. There is considerable evidence of familial prevalence.

There is a general feeling that the ease of contracting the disease varies in different areas. If this is substantiated an additional hazard is presented to our soldiers and sailors assigned to endemic areas. The indefiniteness of the incubation period, ranging as it apparently does from months to years, produces an at present insoluble problem in the matter of continental quaran-

time It would only be those with visible lesions of early leprosy who could justifiably be held for observation for any significant length of time

*Diagnosis and Management*—While the major point in diagnosis may be the finding of acid-fast organisms in smears from lesions and the reasonable demonstration that they are not *Mycobacterium tuberculosis*, the practical recognition of cases of leprosy must still rest on those capable of making a clinical diagnosis For this reason practitioners generally are admonished to suspect leprosy in all not readily diagnosed skin and peripheral nerve lesions and be willing to seek early consultative advice This is particularly true when skin lesions are combined with anaesthesia or paresthesia.

Leprosy is a universally notifiable and reportable disease The inability of the private practitioner to cope with the manifold problems aroused by the discovery of a case makes it imperative that he call upon the authorities for proper disposition of his patient. By the same token his responsibility is increased for the exercise of his greatest diagnostic skill in the diagnosis and handling of suspected cases.

### Relapsing Fever

*Tick-borne*—Tick-borne relapsing fever is the only form of this disease encountered in the continental United States It occurs in the Southwest, particularly in the valley of the Colorado River and in California

The specific parasite, *Borrelia duttoni*, is transmitted in the American form of the disease by the soft-bodied ticks of the genus *Ornithodoros* These ticks breed in the habitats of rodents and bats, but on invading houses and huts behave much like bedbugs The spirochetes liberated from ticks gain entrance through any abrasion or lesion of the skin

Relapsing fever is at present a diagnostic problem only in the endemic areas of the Southwest Were all cases recognized or suspected soon after the onset of rapid rise in temperature, chills and generalized pains, the diagnosis would be readily made, for a blood smear at that time would reveal the causative agent. Delay in examination of the blood may result in negative findings, for the febrile attacks may terminate by crisis in five or six days and the spirochetes disappear from the per



splenic blood The enlargement of the spleen in this condition adds to the possibility of confusion with malaria

Recurrence of the disease after an afebrile period of four or five days may be the cause of the first suspicion that relapsing fever is being dealt with A blood smear at this or subsequent recurrences should confirm the suspicion

*Louse-borne*—Although the louse-borne European and African forms of relapsing fever are not known to exist in this country, there appears to be no good reason why they could not They are caused by spirochetes morphologically identical with those of American relapsing fever but transmitted by the body louse (*Pediculus humanus*) It may be premature to predict the possibility of the introduction of this strain to America and its establishment here Since the differences between the strains are so minor and because the body louse is prevalent in this country, the suspicion exists that, given a sufficient number of unrecognized cases and the proper concentration of susceptibles under conditions of lousiness, this potential importation may become actual

*Control Measures*—It is obvious from this brief discussion that prevention rests on recognition of the cases and personal and domestic hygiene Any personal or large scale measures against the tick or the louse will control the spread of relapsing fever

### Filariasis

The presence up to very recent years of an endemic focus of this disease in and about Charleston, South Carolina, warrants consideration of filariasis among the tropical diseases now present in this country Although this focus may not now exist, cases having their origin in Charleston or elsewhere in the Western Hemisphere are reported from time to time in cities of the United States The presence of returned troops who have filariasis and are now in our military hospitals in this country is further reason for considering it under this category

Classical filariasis with elephantoid swellings is produced by the specific blood filaria *Wuchereria bancrofti* It is spread throughout practically all tropical areas of the world through its mosquito hosts, particularly *Culex quinquefasciatus*, *Culex pipiens* (China) and *Aedes variegatus* (Pacific Islands).

The necessary vectors are present in many areas of the United States and there is little reason to doubt that, given a sufficient number of infected individuals in a community where the proper mosquito host exists and the opportune season for the infection to become widespread in the mosquito population, secondary cases and even endemic foci might become established. The lesson of immediate importance to be learned from the epidemiology of this disease is that troops with filariasis returned from endemic areas must not be hospitalized in localities where potential mosquito hosts exist and that they must be prevented from being bitten by mosquitoes.

*Diagnosis*—Until the lymph blockage begins to reach the clinical stage, filariasis may be present without any symptoms. This symptom-free period is of variable length and may be sufficiently long to extend beyond the ordinary quarantine period for other infectious diseases.

The presence of unexplained swellings of any kind on any parts of the body of exposed individuals warrants a search for microfilariae in the peripheral blood. In this species, the microfilariae migrate at night so that the search by means of peripheral blood smears should be made around midnight.

*Prevention and Treatment*—There is no present known specific treatment for the disease but sulfadiazine has been recommended. Prevention involves every known measure for mosquito control.

## II TROPICAL DISEASES FORMERLY BUT NOT NOW PRESENT IN THE UNITED STATES

### Yellow Fever

The last recognized case of yellow fever in the United States occurred in 1905. Since that time the Gulf States have maintained a particularly sharp vigilance against its re-introduction from endemic areas in South America. The acceleration of travel by means of airplane has sharpened the precautions taken by the United States Public Health Service. This country is by no means removed from the danger of resurgence of this disease in epidemic proportions. Insofar as is known, the population of the United States has for many years been theoretically 100 per cent susceptible. The few persons in the Gulf States who may

have developed immunity prior to 1905 may be ignored. Within recent months many of our armed forces have received protective vaccination but for practical purposes these too need not be considered, for an unknown number have left these shores.

While it cannot be said with assurance that yellow fever is a potentiality wherever the vector (*Aedes aegypti*) of the virus exists, it can be assumed that epidemic yellow fever will not occur where this mosquito is not present. Historically, yellow fever has appeared in epidemic proportions throughout the southern and eastern Middle Atlantic coastal plains and it might possibly appear again.

*Control Measures*—Mosquito control and quarantine have been the measures responsible for the eradication of yellow fever from this continent. To these may now be added preventive immunization. Thus the prevention of this disease approaches the ideal, a potentially immune population, sufficient knowledge of the vector to enable its effective control, and efficient quarantine service both at the point of embarkation and debarkation of immigrants.

*Diagnosis*—It is impossible within the scope of this presentation to give adequate information regarding the clinical aspects of this disease and the measures necessary for its recognition and diagnosis. That it is an acute febrile disease characterized by jaundice, albuminuria, bradycardia and severe liver damage can hardly suffice. Treatment is only symptomatic and cannot be covered adequately here. There is moreover no diagnostic test readily available to practitioners or within the routine possibilities of most laboratories. Whenever suspected it should always be reported immediately.

It remains therefore only to point out that every fever with jaundice should be thoroughly investigated. Confusion is most likely between yellow fever, infectious jaundice (leptospiroid jaundice) and acute catarrhal jaundice. In the case of the latter, special difficulty may be encountered when added zeal on the part of a physician results in a positive test for yellow fever (mouse protection test) in a patient with catarrhal jaundice who has been previously immunized with yellow fever vaccine! There may be many such among our returning troops.

## Plague

This acute infectious disease has, in the course of history, been present in almost all countries and left behind it rodents infected with *Pasteurella pestis*. This appears to be true in this country, particularly in the Central and Northern States west of the Rocky Mountains.

Strictly speaking, this disease should be included among those still present in the United States but the conditions under which the infection persists in the rodent population without other than a few accidental cases among humans makes it reasonable to discuss it here. This is particularly true in respect to the country as a whole, for the Eastern seaboard where it formerly appeared in such intense epidemic proportions is now, so far as known, free of even the rodent form. Conditions apparently exist on this continent which make its spread to the human population possible whenever the factors responsible for its transmission become favorable. As with yellow fever and cholera, the soil is ripe but the spreading of the seed has been prevented by active measures against it. The most effective measure has been rat control.

Epidemics of plague are usually of rodent origin. Infected rats, squirrels, marmoset or other rodents develop periodic epizootics. The rat flea transmits the causative agent, *Pasteurella pestis*, by its bite, to man. The primary bubo of bubonic plague is the regional lymph node swelling following the flea bite, septicemic plague is the blood-stream infection with the same organism, pneumonic plague is the secondary pneumonia developing in one of the previous two forms or resulting primarily in the lungs following inhalation of infected droplets from a contact case of plague pneumonia.

**Control Measures**—There is at present no alternative to the control of plague by antirodent and flea extermination other than by the supplemental use of plague vaccine. In the Far East, particularly in Java, and more recently in Africa, widespread use is made of Otten's attenuated living vaccine, while in India, China and most other threatened areas Haffkine's killed vaccine is used. In either case the consensus seems to be that annual vaccination is necessary and that periods of effective immunity longer than a year are not reliable or obtainable.

The reader must be referred to more exhaustive works for all of the detailed procedures involved in the protection of ships, warehouses and dwellings from infestation with rats and for the various insecticides and fumigants for the eradication of fleas.

The current speed-up in communications makes it imperative that there be no let-up in the splendid national and international quarantine agreements against the spread of plague. No country can afford to neglect the potential hazards of this devastating disease and continued concerted action by all nations is necessary for its control.

### Cholera

The level of sanitation in the United States is almost complete assurance that this presently exotic disease could not gain a hold in any representative community of this country.

Cholera is so much a disease of massed populations under unsanitary conditions that only the most serious breakdown in our quarantine, and concurrent let-down somewhere in sanitary precautions would permit its introduction here.

Nevertheless, vigilance must be continued because of uncertainties brought about by the speed of travel and the consequent nearness of the Orient.

*Control Measures*—Aside from quarantine law enforcement and the maintenance and improvement of sanitation in some backward areas of this country, the best precaution against reintroduction of cholera into the United States will rest on individual hygienic measures and the use of protective immunization.

Cholera is the story of fecal contamination of food and water. The cholera vibrio is a water-breeder and can exist in any polluted water supply. Vegetables and fruits may readily become secondarily contaminated from impure water in which they are grown, washed or improperly prepared for eating. In endemic cholera areas no fresh fruits or vegetables should be eaten unless they have been thoroughly washed with clean water or antiseptic solutions such as potassium permanganate, or scalded. Fruits that must be peeled to be eaten are safe inside but may be contaminated outside, the act of peeling such an unwashed fruit may itself contaminate the edible interior.

Vaccination against cholera is effective but not lasting and

should not be depended upon for a period longer than four to six months. Usually an annual reimmunization is sufficient in those areas where the cholera season comes once a year.

The arrival of a cholera patient at our seaports or points of landing of airplanes from endemic areas is not an impossibility. The abrupt onset of diarrhea, vomiting, rice-water stools and dehydration should be sufficient impetus to make any physician in charge go into immediate action and look for vibrios in a hanging drop from the watery stool.

### III TROPICAL DISEASES NEVER KNOWN TO HAVE BEEN PRESENT IN THE UNITED STATES

#### African Trypanosomiasis (African Sleeping Sickness)

The tsetse fly (*Glossina palpalis* and *G. morsitans*) is the only known carrier of the trypanosomes (*Trypanosoma gambiense* and *T. rhodesiense*) responsible for sleeping sickness. This fly is unknown outside of Africa and Arabia and for this reason alone trypanosomiasis could hardly be permanently introduced into this country.

Interest in African sleeping sickness in America centers around the likelihood of cases in the preclinical period of the disease being returned to the United States. Since this period varies from ten days to three weeks or more, this is a possibility.

Those concerned are cautioned in regard to the possible introduction of tsetse flies into this country similar to the way in which *Anopheles gambiae* was brought into South America. Safety beyond this point seems to rest in the less likely possibility that large animal reservoirs might be developed here.

**Diagnosis**—Recognition of sleeping sickness depends largely on the presence of an undiagnosed febrile condition characterized particularly by remittent fever with rapid pulse, neurologic symptoms of varying degree and manifestations ranging from tremors and hyperesthesia to marked psychotic states and somnolence. One of the outstanding characteristics is soft, elastic enlargement of the posterior cervical glands.

When the question of diagnosis arises, trypanosomes may be recovered from the enlarged glands and may be found in thick blood films or spinal fluid.

**Treatment**—Tryparsamide and Bayer 205 are the drugs of

choice in Gambian or West African forms of the disease while Bayer 205 (Naphuride, Winthrop) is used in the Eastern or Rhodesian type.

### American Trypanosomiasis (Chagas' Disease)

The title "American" applied to this disease at present means South and Central American. The transmitting agent is the cone-nosed kissing bug *Panstrongylus megistus* (*Triatoma megista*). This bug is present in California and the southwestern United States. It lives in rodent burrows, particularly those of armadillos and opossums, and enters human habitations where it bites its human victims. The bite of the bug is relatively painless and may not awaken the sleeper. Scratching of the bite inoculates the skin with trypanosome-bearing feces that is habitually deposited by the bug in the act of biting.

The animal reservoirs of the disease are armadillos, opossums and other wild rodents. These animals as well as the reduviid bugs have been found infected with trypanosomes under natural conditions in the areas mentioned above.

Chagas' disease is a serious disease of high mortality among children. The trypanosomes produce fever, facial edema and adenitis in the acute stage and cardiac, thyroid, or central nervous system derangements later.

It is obvious that in the United States the disease would be likely to occur only in those areas where the *Triatoma* exists, inhabits rodent burrows where animal reservoirs have been established and where the living and sleeping habits of the people are such as to permit so large an insect as this to gain access to them while sleeping at night. At present these possibilities appear to exist only in areas where the inhabitants live in adobe huts under low economic conditions. Prevention is obvious.

There is no known effective treatment or specific preventive for Chagas' disease.

### Visceral Leishmaniasis or Kala-azar

*Leishmania donovani* is known to exist at present in the Mediterranean area, through India and China, and in South America in Eastern Brazil, the Matto Grosso region of the Paraguay-Brazilian border and in Bolivia. The most likely transmitting agent is the sandfly (*Phlebotomus*) although there is

evidence that it may be transmitted by contact or by contaminated food

Kala-azar is pathologically a blocking of the reticulo-endothelial system. Its important manifestations of marked splenomegaly, anemia and leukopenia with monocytosis are evidences of this disturbance.

An important characteristic of the distribution of visceral leishmaniasis is its marked tendency to limitation to geographic areas by some still unknown factors. Possibly the conditions for propagation by the sandfly are important in this consideration.

No sandfly vector has been identified in the United States and there exists no reason to believe that visceral leishmaniasis will become a disease of this country.

Cases of kala-azar may be seen later in this country in troops returning from infected regions of Asia, Europe and South America. As such they might constitute a serious problem in diagnosis requiring differentiation from other chronic diseases characterized by splenomegaly and anemia. Definite diagnosis can only be made by finding leishmania in smears from spleen or bone marrow puncture.

#### Cutaneous Leishmaniasis or Oriental Sore

Most that has been said about kala-azar applies to oriental sore insofar as etiology, transmission and distribution are concerned. The specific leishmania is *Leishmania tropica*. Although it exists in most countries where *L. donovani* is present (except South America) there is a tendency for the two organisms to remain discrete in localized areas.

Should it become more firmly established that oriental sore can be spread through direct contact, secondary cases might occur for a while wherever patients with undiagnosed ulcers are permitted to move freely in the population. This would seem to be reason enough for physicians generally to suspect and look for leishmania in recalcitrant ulcers of unknown etiology in returned troops.

#### American Mucocutaneous Leishmaniasis (Espundia)

The American form of leishmania responsible for this ulcerating condition about the nose and mouth is *L. braziliense*. Like



the other leishmanias it is believed to be carried by the sandfly or spread by contact. The disease is widespread through northern South America and occurs in Central America as far north as Mexico.

A cautious watch should be kept on all undiagnosed ulcerative lesions (goundou) around the nose and mouth of persons returning from endemic regions. Leishmania should be sought for in smears from these sores.

### Schistosomiasis

The schistosome flukes producing disease in man are of three species and distributed as follows:

*Schistosoma mansoni*—North Africa, northern countries of South America and many islands of the West Indies.

*Schistosoma haematobium*—the African-Mediterranean area, Abyssinia, East, West and South Africa, the countries of the Middle East and the islands of Madagascar, Mauritius and Reunion.

*Schistosoma japonica*—predominantly found in the valley of the Yangtze in China, the Mekong River Valley of South China and Indo-China and in Japan, Formosa and the Philippine Islands.

All of the schistosomes have a life cycle involving specific forms of snails, and the propagation of the disease in any region is conditioned by the presence of the specific invertebrate host, conditions of the environment favorable to the persistence of the developmental forms of the schistosome both while in the snail and in its free-living state in water sources, and the social habits and customs of the people that bring them into contact with infective forms in these water sources.

No evidence exists that such conditions are present in the United States, and the establishment of any form of schistosomiasis as an endemic disease of this country is hardly to be considered. On the other hand, imported case of schistosomiasis may reasonably be seen here.

**Diagnosis**—*Schistosoma mansoni* infection must be differentiated from many chronic conditions characterized by ulcers and fistulas about the colon and rectum, bloody stools, ascites and hepatic cirrhosis. *Schistosoma haematobium* is to be suspected in patients coming from endemic areas who present

symptoms referable to the genito-urinary tract particularly hematuria, bladder ulcers and papillomas, and late cirrhotic changes in the liver *Schistosoma japonica* may produce vague intestinal manifestations but will more likely be encountered in the stages of liver cirrhosis and splenic enlargement

When suspicions are aroused in any undiagnosed case which presents symptoms such as the above and the patient has been in an endemic area of the disease, the presence of the characteristic eggs of each species must be looked for

In *S. haematobium* infection the terminal-spined eggs are to be found in the urine or feces, or both, in *S. mansoni*, lateral-spined eggs appear in the feces and rarely in the urine, while the spineless eggs of *S. japonica* occur only in feces

#### Yaws (Frambesia)

This is a chronic infectious spirochetal disease caused by *Treponema pertenuis*. It is transmitted by direct contact in most instances but may be mechanically carried from person to person by common flies. It is nonvenereal.

The disease is well established in the West Indies and the coastal area of Colombia but in spite of its ease of spread has never been present in continental United States. It is a common disease of Africa, Southeast Asia, the Philippines and the Polynesian Islands.

Yaws develops as an initial lesion on some exposed part of the body as a granulating papilloma known as the mother yaw, and in the course of a few weeks appears on other parts of the body as daughter yaws. A yaw cleaned of its superficial crust presents small elevated proud-flesh-like granules with yellowish white tips giving it the appearance of a raspberry from which the name of the disease, "frambesia," is derived.

Extensive involvement of the mucous membranes and subsequently the submucous tissues and bones of the nose, mouth and palate may occur, giving rise to the disfiguring destructive ulcerations and necrosis of these parts known as *gangosa*. Similar destruction of soft tissues in the anal region results in anal strictures.

*Diagnosis* of yaws is made by dark-field examination of the tissues and the finding of the specific spirochete. The Wassermann test usually becomes positive sooner or later.

Mild *antisyphilitic treatment* by means of the arsenicals usually results in rapid and complete cure of the disease

### CONCLUSION

The tropical diseases considered here are all of immediate concern to every physician in this country. Those conditions already with us must be recognized, controlled and eliminated by the concerted action of our entire medical profession. Tropical diseases once existing here can recur if we permit our standards to revert in any community to those under which they formerly thrived. The exotic diseases beyond our continental boundaries may become of immediate concern to any physician called upon to diagnose and treat their unfamiliar manifestations in service men or civilians returning to their home communities from foreign travel.

The young doctors among us may find themselves facing the problems of many diseases of foreign lands within a matter of months, weeks or even days.

On our profession as a whole and on the official agencies particularly, falls the immediate necessity to be aware, to overestimate rather than underestimate our potential dangers and to exert every effort to maintain our high health standards in this country.

Every physician should be informed by literature and any other practical means of the tropical diseases of concern to the home front, he must at least know to whom to turn for help when he needs it.

# THE MENINGITIDES AND ENCEPHALITIDES

ALISON H PRICE M D \*

## THE MENINGITIDES

PURULENT meningitis has always been a medical emergency and with the exception of meningococcus meningitis, the prognosis has been extremely poor. The case mortality rate for those who developed acute purulent meningitis was over 90 per cent. The use of sulfonamide compounds has lowered the mortality rate appreciably, but has not detracted from the emergency which exists when a case of purulent meningitis is encountered.

Diagnosis depends on the following clinical observations and laboratory findings: (1) sudden onset, (2) headache, (3) malaise, (4) fever, (5) nausea and vomiting, (6) stiff neck, (7) positive neurological signs, (8) increased intraspinal pressure, (9) changes in the cerebrospinal fluid and (10) demonstration of the causative micro-organism.

Arranged in the order of frequency the more common bacteria causing acute purulent meningitis are: (1) meningococcus, (2) *Streptococcus hemolyticus*, (3) pneumococcus, (4) influenza bacillus and (5) staphylococcus.

The meningococcic infection is found most frequently in the epidemic form and when one of the other organisms is the cause, the meningitis is usually sporadic or secondary to pneumonia, empyema, abscess, peritonitis, otitis media, pericarditis, sinus infection, injury or operation.

## MENINGOCOCCIC MENINGITIS

Meningococcic meningitis (cerebrospinal fever, epidemic meningitis) occurs in sporadic and epidemic forms. The epidemics are irregular in appearance and are apt to be more severe during war. They involve both military and civilian populations. There were thousands of cases of meningococcic meningitis during the World War I and during the present war there have

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\* Ross V Patterson Fellow in Medicine, Jefferson Medical College and Hospital

been large epidemics in England. In this country the increase in the number of sporadic cases has reached epidemic proportions, however, the incidence rate of the disease at the peak has been below the peak rate of 1917-1918.

**CLINICAL PICTURE**—*Headache* is the most common and earliest symptom of meningitis regardless of cause. The headache of meningitis is often intense and agonizing. The onset is usually sudden with *malaise*, high or gradually rising *fever*, and *stiffness of the neck*, slight at first, increasing as the disease progresses and often causing retraction of the head. Other signs common in meningitis are dizziness, convulsions, restlessness, insomnia, vomiting, drowsiness, stupor, petechiae or purpura and finally coma and delirium.

The *petechiae* or purpura are noticed more frequently during epidemics and are most marked in the fulminating septicemic forms when there may be large hemorrhagic areas scattered over the body. Meningococci have been cultured or seen in direct smears from these purpuric lesions of the skin.

The positive *signs* usually found are Kernig's, Brudzinski's and contralateral Brudzinski's, and in a variable number of cases Babinski's sign. The pulse is slow (bradycardia) in proportion to the temperature elevation. The leukocyte count of the blood is elevated early and is from 15,000 to 35,000 per cu mm.

**DIAGNOSIS**—In all patients the *cerebrospinal fluid* should be examined. The cerebrospinal fluid is removed aseptically by inserting a needle in the area between the third and fourth lumbar vertebrae. If local anesthesia is used, infiltration of the skin is all that is necessary. Care must be taken not to inject any of the anesthetic agent into the spinal canal. Cocaine hydrochloride and nupercaine are preferable to procaine hydrochloride as the latter inhibits the action of the sulfonamide compounds. Whenever possible the initial spinal fluid pressure should be measured. The spinal fluid pressure, if increased, should be slowly reduced, drop by drop, to approximately a normal figure. For examination, 5 to 10 cc of spinal fluid is collected in each of two sterile test tubes with rubber or cork stoppers. The collected fluid is smeared on a glass slide and stained with Gram's stain. To stain with methylene blue is only adding another step. A differential cell count of the stained smear should be done to classify the types of leukocytes and to find intracellular or extracellular

bacteria The presence of stained bacteria on the slides is not sufficient, however, for a final etiologic diagnosis, which can be based only on fermentation reactions and serologic identification The total cell count should be made very soon after the spinal fluid is collected, as cells soon stick together and to the sides of the tube, making later counts inaccurate If a clot forms, an accurate cell count is impossible

Blood agar heated to form chocolate agar is especially convenient for direct *culture of the spinal fluid* at the time of the lumbar puncture It supports the growth of all the organisms commonly causing meningitis The media should be warm and should be streaked immediately on a plate, placed in an incubator or transported to the laboratory in a heated box Cox, McDermott and Mueller have shown, however, that meningococcal material for culture can be preserved for two or three days over a considerable temperature range by immersing the swab in a few drops of sterile horse blood, thus making possible shipment of specimens through the mail and materially simplifying the manner of examination of carriers in the field

*Blood culture* should also be made early The blood should be obtained by aseptic venous puncture at the bedside Approximately 10 cc of blood is injected into a flask containing 100 cc of effusion broth Growth of meningococci is shown by clouding of the broth media or partial hemolysis of the blood and occurs in from twenty to seventy-two hours When the patient has received one of the sulfonamide compounds prior to study, it is necessary to add para-aminobenzoic acid, 5 mg per 100 cc of culture media This prevents the sulfonamide compound from acting on the organism being cultured When there is any growth the organism should be preserved for future reference.

**TRANSMISSION**—Transmission is from man to man It is often difficult to trace direct contact between cases of meningococcic meningitis The difficulty is probably the result of the relative immunity to the meningococcus of a large percentage of the population If they have harbored the organism at one time or another and developed some immunity, they may be healthy carriers of a virulent strain and may pass this organism through a long chain of individuals before it reaches one in which the conditions for invasion are ideal When this patient becomes ill, it is often impossible to trace the intervening chain of passage.

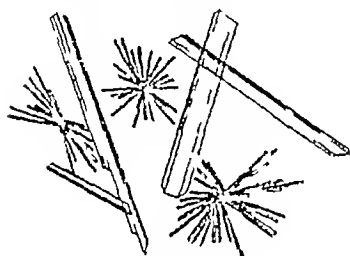
**PROPHYLAXIS**—The patient with meningococcic meningitis should be isolated. The problem of treating carriers is unsettled. However, Mueller took approximately 400 individuals and gave one-half of these sulfadiazine for three successive days 3 gm. on the first day and 2 gm. on each of the following days, and the other half of this group of 400 served as controls. Three days after the administration of the drug, nasopharyngeal cultures of all 400 individuals were taken. In the control group type I carriers had increased from 68 to more than 70 per cent, but of the 200 who had received sulfadiazine not a single one carried meningococci. Based on these findings it might be advisable in epidemics of meningococcic meningitis to treat contacts with doses of sulfadiazine, and in an emergency it may be possible to eradicate carriers in a given group of individuals.

**TREATMENT**—*Lumbar puncture* is done when the patient is first seen, both as a diagnostic measure and as treatment to relieve increased intraspinal pressure. The reduction of pressure will in many cases alleviate the patient's headache and restlessness and make the nursing care much easier. The lumbar puncture is repeated six hours following admission if the patient is still restless and uncooperative and complaining of agonizing headaches, otherwise, it is not repeated unless the patient fails to respond to treatment or there are signs and symptoms of a relapse. If delirium, restlessness and headaches are not relieved by repeated lumbar punctures, paraldehyde, barbiturates, codeine sulfate, and even morphine sulfate have been advised.

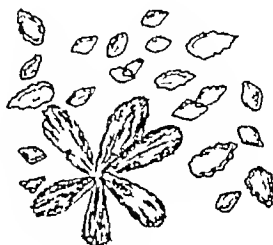
The introduction of the sulfonamide compounds in the treatment of meningococcic meningitis has not detracted from the great importance of *good nursing care* which every patient needs. If the patient has urinary retention, catheterization may be necessary. Care must be taken by the nursing staff to prevent the development of bed sores and the mouth and eyes need constant attention. The patient must be given a nourishing diet and if his urinary output falls below 1000 to 1500 cc., fluid intake must be increased either orally or intravenously. A solution of physiological sodium chloride is satisfactory for intravenous use, however, if it is necessary to give more than 2000 cc. of fluid to equalize the water balance, alternate injections of 5 or 10 per cent glucose in distilled water are advocated.

**Chemotherapy**—In the treatment of meningococcic menin-

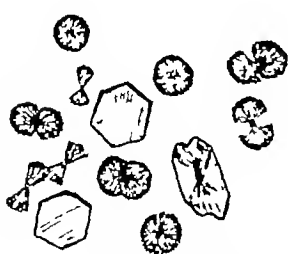
gits the sulfonamide compounds are highly efficacious Sulfanilamide, sulfapyridine, sulfathiazole and sulfadiazine have all been used with success, but sulfadiazine is the least toxic and is the drug of choice. If sulfapyridine, sulfathiazole or sulfadiazine is to be given intravenously, the sodium salt may be used A 5 per cent solution of the sodium salt is recommended These salts are highly alkaline and care must be taken that the solution does not escape into the tissues



SULFANILAMIDE



SULFAPYRIDINE



SULFATHIAZOLE



SULFADIAZINE

Fig 145—Sulfonamide crystals in the urine

The initial oral dose is 4 gm. (60 grains) and subsequent doses of 1 gm (15 grains) are given every four hours day and night until the temperature remains normal for five days It is satisfactory and it has been our practice to give the initial dose intravenously as in this manner a high blood level is obtained more rapidly than is possible with administration by mouth Furthermore, this method is applicable to those patients who



have nausea and vomiting in whom it is impossible to give the drug by mouth. An injection is made of 5 or 6 gm of sodium sulfadiazine in 100 cc of distilled water. This is followed in six hours by an additional 3 gm of the sodium salt intravenously and starting at that time 1 gm of sulfadiazine every four hours by mouth. This averages approximately 6 gm per day for adults. For infants and children 0.1 gm per kilogram of body weight per day is given. A blood level of approximately 10 mg per 100 cc should be maintained with the sulfonamide compounds. The urine should be examined daily for the presence of sulfonamide crystals (Fig 145). The determination of the drug level in the cerebrospinal fluid is not important. As mentioned, 1 gm of the sulfonamide drug every four hours is continued orally for five days after recovery has occurred and the temperature has returned to normal.

The sulfonamide drugs should not be given intrathecally. They may be given subcutaneously as recommended by Taplin and his associates, using a concentration of approximately 0.3 to 0.7 per cent solution, that is, from 3 to 7 gm of the sodium salt in each liter of a physiological solution of sodium chloride. These concentrations of the sodium salts may be given without fear of causing local necrosis or slough.

*Serum*—If the patient fails to show improvement following forty-eight hours of adequate chemotherapy with one of the sulfonamide compounds, then antiserum may be used which contains antibodies for the type of meningococcus present. At the present time only two groups of meningococci need be considered, namely, group I which includes types I and III and group II which includes all the remaining types. The meningococci may be identified in a manner similar to the Neufeld reaction used in typing pneumococci, or if this method is not satisfactory the serological identification of the meningococcus may be accomplished by agglutination tests. If the specific antiserum is not available, the polyvalent serum may be used.

If one is prudent the following directions must be followed when giving serum:

1. The patient or family should be questioned for possible sensitization, such as history of asthma, angioneurotic edema, hay fever, sensitivity to horse dander, rabbit hair or injections of serum more than seven days previously.

2 Before injecting any serum, tests to determine sensitization are in order

3 A hypodermic stimulant must be at hand (epinephrine hydrochloride 1 1,000)

4 The serum should be at hand or room temperature *Do not heat*

5 Injection should be slow

The amount of serum necessary to give an excess of antibodies may vary from 20 cc to as much as 100 cc There is no convincing evidence that the intrathecal administration of serum is of any value and as it may be harmful it is not recommended There is no substantial evidence to support the use of antitoxin

COMPLICATIONS—Sequelae and complications are deafness, ocular palsy, strabismus, optic neuritis and changes in mentality The complications which occur or result whenever serum is given with therapy or which may be common with chemotherapy may also be seen when the patient is being treated with either or both of these agents If a relapse or recurrence takes place the patient should be treated as though he or she were a new patient and serum used if indicated

#### STREPTOCOCCUS HEMOLYTICUS MENINGITIS

*Streptococcus hemolyticus meningitis* is seen most frequently with mastoiditis and otitis media

DIAGNOSIS—Diagnosis is dependent upon the signs and symptoms of meningitis plus a history of positive physical findings of foci of infection particularly involving the ear, mastoid process, paranasal sinuses, nose, jaw or teeth, and the presence of hemolytic streptococci in the spinal fluid

PROPHYLAXIS.—The routine use of sulfonamide compounds in patients with acute otitis media and mastoiditis seems of value It is advisable to start chemoprophylaxis at least twenty-four hours prior to operation for mastoiditis and to continue this drug for one to two days after the operation The same procedure may also be used in operations for brain abscess.

TREATMENT—The mortality rate has been greatly reduced by the use of the sulfonamide compounds Sulfadiazine is the drug of choice, then in turn come sulfapyridine and sulfanilamide As in treating all patients with meningitis, a high blood level seems to be of some advantage and should be approxi-

mately 10 mg per 100 cc The drug should be continued for eight days after the spinal fluid becomes sterile and all other evidence of infection has subsided (for dosage and methods of administration see Meningococcic Meningitis). During treatment the blood count should be checked frequently, the level of the sulfanilamide compound should be determined daily and the urine examined for red cells and crystals of the particular sulfanilamide compound being used (Fig 145) If anemia becomes marked, due either to the treatment or to the hemolytic streptococcus infection, small blood transfusions (200 to 300 cc) should be repeated daily or on alternate days as indicated by the erythrocyte count Care should be taken to see that the blood is typed and cross-typed before each transfusion The value of specific serum and of immunotransfusion is still in doubt If in the future the streptococci are grouped and typed and specific serum for each type is available, it may be of some value as an adjuvant to sulfonamide therapy.

Penicillin (filtrate of broth culture of *Penicillium notatum*) is effective in hemolytic streptococcus infections and has the advantages of being relatively nontoxic, highly soluble, nonhemolytic and is active in the presence of pus and para-aminobenzoic acid Unfortunately, bacteria may become penicillin-fast The value and limitations of penicillin are not yet determined, however, it appears promising

#### PNEUMOCOCCIC MENINGITIS

Pneumococcic meningitis is rarely primary, but occurs after injury of the head, pneumonia or other infections of the respiratory tract and may be a complication following septicemia, otitis media, mastoiditis and sinusitis Pneumococcic meningitis following pneumonia has an extremely poor outlook and if endocarditis develops with evidence of a bacteremia, the disease is fatal in almost every case Although it has been said by some that the mortality rate since the advent of sulfanilamide compounds has been about 35 per cent, unfortunately it has been our experience that this is entirely too low and that the mortality rate in cases of pneumococcic meningitis is nearer 85 per cent

DIAGNOSIS—Diagnosis is dependent upon the signs and symptoms of meningitis plus a history of pneumonia, septicemia, otitis media, mastoiditis or sinusitis and the presence of the pneumococcus in the spinal fluid

**PROPHYLAXIS**—The prevention of exposure, the prompt treatment of lobar pneumonia and the routine use of sulfonamide compounds in patients with otitis media and mastoiditis comprise the prophylactic measures

**TREATMENT**—Sulfadiazine is the drug of choice and high blood levels (10 mg per 100 cc) should be maintained (See Chemotherapy under Meningococcic Meningitis) The drug is continued for fourteen days after the cerebrospinal fluid becomes sterile and after all evidence of infection has completely subsided When the pneumococcus is isolated it should be typed and type-specific antipneumococcic serum may increase the chance for recovery As therapeutic rabbit serum is now available for almost all the types of pneumococci encountered, type-specific antiserum should be given intravenously, 200,000 units as the initial dose (see precautions under Treatment of Meningococcic Meningitis, page 1502) The antiserum should be given slowly in one injection over a period of five or ten minutes Additional doses of 100,000 units should be given every twelve hours until a positive balance of antibodies is obtained and maintained I do not believe that intrathecal administration of serum is of any proved worth In numerous cases relapses occur after patients are apparently cured, and in the majority of these they fail to respond to any further treatment

#### INFLUENZA BACILLUS MENINGITIS

(*Hemophilus influenzae*)

Influenza bacillus meningitis is seen most frequently in children and infants Almost all affected children under the age of two years die Treatment in older patients seems to result in a lower mortality rate The organism may be found in the bloodstream early in the disease When seen in the spinal fluid, it is a tiny, pleomorphic gram-negative bacillus which can be seen on direct smear The type of influenza bacillus can be determined by the capsular swelling when the specimen is treated with specific rabbit antiserum, or by precipitation with the use of clear supernatant spinal fluid There are six known types of influenza bacillus, which are immunologically distinct, and they are classified as types a to f Of these, type b produces a great majority of infections in children

The value of sulfonamide compounds in the treatment of

influenza bacillus meningitis is not proved. Those patients reported as having recovered are for the most part in the older age group in which occasional spontaneous recovery occurs. Recently, rabbit antiserum specific for type b influenza bacillus has been used with encouraging results. If the organism is type b, intravenous serum therapy should be employed in the early stages. If the organism is not type b or cannot be typed, then one of the sulfanilamide compounds, preferably sulfathiazole, should be used in doses as outlined under Treatment of Meningococcic Meningitis.

It is suggested by some that if the patient fails to respond to the intravenous administration of serum, the intrathecal administration of antiserum and complement should be considered, however, I do not believe that the present value of this procedure justifies its use.

#### STAPHYLOCOCCIC MENINGITIS

Staphylococcic meningitis is usually preceded by a history of an abscess or other foci of infection. Sulfathiazole appears to be the drug of choice, however, the treatment of this disease is not satisfactory at the present time. It has been suggested that because there is tendency for the staphylococcic infection to recur or to become chronic, therapy with the sulfonamide compounds should be continued from two to four weeks after the infection has cleared. Dosage and routes of administration for the sulfanilamide compounds were given previously under Meningococcic Meningitis.

It has been advocated by Julianelle that staphylococcus antiserum may be used in cases resistant to the drug or as a supplement to sulfonamide therapy. The average total dose ranges between 80 and 200 cc of serum. It has been suggested that 60 cc be given on the first day, 40 cc on the second day and 20 to 40 cc on subsequent days. The antitoxin is not of proved worth.

Penicillin may eventually prove to be most useful.

#### THE ENCEPHALITIDES

A list of the known forms of primary encephalitis, particularly those caused by filtrable viruses, is as follows: St. Louis encephalitis, Japanese encephalitis, Russian encephalitis, eastern equine encephalitis, western equine encephalomyelitis, lympho-

cytic choriomeningitis, poliomyelitis, lethargic encephalitis, (Von Economo or Vienna type), rabies, West Nile Fever, lymphogranuloma venereum and herpes simplex. One may gain the impression from this classification that the matter of etiologic diagnosis of encephalitis is an easy one and that most cases fit into one or another entity. In a great majority of sporadic cases, however, an etiologic diagnosis cannot be made with the knowledge and technic now available. The response of the central nervous system to the neurotrophic virus is of such a uniform nature that the clinical and pathological features of most of the virus encephalitides are so similar that it is usually impossible or difficult to make an etiologic diagnosis without laboratory help. With numerous outbreaks of encephalitis, the following may be helpful for classification: (1) distribution of cases according to age, sex and occupation, (2) seasonal incidence, (3) neurological residuals or cranial nerve palsy, (4) spinal fluid examination for number and type of cells, and (5) mortality rate. The course of the patient's illness, regardless of the etiologic agent, may vary from headache, malaise and slight fever lasting a day or two to the extreme case in which death may occur twenty-four to forty-eight hours after onset.

#### ENCEPHALITIS LETHARGICA

(Epidemic Encephalitis Von Economo's Type of Encephalitis)

The etiologic basis of this disease is not known, but is believed to be a virus. While this illness may occur in any season, it is the only one of the encephalitides which has occurred as an epidemic during the winter months. No age is exempt, although the incidence appears to be greater in the age group of ten to forty-five years.

**CLINICAL PICTURE**—The onset may be sudden or gradual and the symptomatology depends upon the parts of the brain involved. The patient may not be sufficiently ill to be bedfast or the infection may be overwhelming and the patient die after a brief illness. The symptoms are chiefly headache, lethargy, malaise, stiffness of the back and diffuse pain. Fever is usually present and it may be brief or last for weeks. High fever has a bad prognostic import. Approximately three-quarters of the cases show lethargy. In these the patients are easily aroused and seem to be rational for time and place. Almost one-half of the

cases show eye symptoms Among these are strabismus, photophobia, nystagmus, ptosis and blurred vision

**DIAGNOSIS**—Diagnosis is frequently arrived at from the symptoms and signs of encephalitis with normal spinal fluid protein and sugar The cell count of the spinal fluid may be slightly elevated or normal and the pressure at times is elevated The differential diagnosis of an intracranial lesion is definitely ruled out by the physical findings and the lack of changes in the optic fundi Diagnosis is based upon (1) lethargy, (2) eye symptoms, (3) prolonged course, (4) chronic manifestations, particularly parkinsonism, (5) negative serological test with a known virus infection, and (6) negative Wassermann reaction The patient may make an uneventful recovery or he may progress into the chronic form and develop ocular motor palsy and other neurological residuals, among which are parkinsonism, tremor, rigidity and oculogyric crises

**TREATMENT**—Treatment for these patients is symptomatic The patient should be kept warm, the fluid intake should be 3000 or 4000 cc for twenty-four hours and the diet should be liquid or soft In the acute cases the patients should be isolated, since there is some question as whether or not the disease is spread by contact Repeated lumbar punctures and the intravenous use of hypertonic salt solution or a 50 per cent glucose solution helps to relieve headache and to diminish the drowsiness in the early stages when the spinal fluid pressure is increased Nocturnal restlessness may be treated with chloral, barbitol, or phenobarbital Hypersomnolence, if marked, must be treated by nutritional maintenance with the stomach tube, by intravenous therapy, or by hypodermoclysis If convulsions are persistent it may be necessary to use intravenously one of the barbiturates, either sodium amytal, 0.2 to 0.5 gm (3 to 7½ grains), or sodium luminal, 0.9 gm (1½ grains) If paralysis occurs with bladder and bowel incontinency, great care must be taken with the patient An indwelling catheter with tidal drainage is indicated, he should be kept dry and all possible precautions should be taken to prevent bed sores He should occasionally be rolled from side to side in bed

Treatment of the *neurological residuals* is as follows For the postencephalitic parkinsonism, atropine sulfate in an 0.5 per cent solution is given by mouth. Adults receive 1 drop in water

three times a day as the initial dose, and the dosage is not increased too rapidly. At the end of five days this may be increased to 2 drops three times a day and another tolerance period maintained. This gradual increase in dosage is continued until the optimal point is reached, this may be from 6 to 15 or 20 drops three times a day. If the patient develops blurring of the vision, flushing, diarrhea, palpitation or retention of urine the drug must be stopped for a few days and started again at a lower dosage. If the patient is unable to tolerate the atropine or belladonna, syntropan, a synthetic drug with the characteristics of atropine, may be used. This is first given in a dosage of one 200-mg tablet three times a day, the dosage later being gradually increased. It may be continued for a long period of time, but is not quite as satisfactory as atropine. For tremor, stramonium may be given as tincture of stramonium, 1 cc or 15 drops three times a day, the dosage being gradually increased until 50 to 75 drops a day are being given in three doses. Benzodrine sulfate has been suggested in doses of 10 mg once to four times daily. It is of little value, however, since the small doses are ineffectual and large doses disturb the patient's sleep. In young subjects and older patients who are good operative risks and in whom the persistent tremor is not controlled by drugs, operative treatment must be considered. One of these operations is the removal of the opposite premotor cortex. This leaves no residual paralysis, but results in a loss of the tremor.

#### ST LOUIS ENCEPHALITIS

(Epidemic Summer Type of Encephalitis)

The St. Louis type of encephalitis is a virus disease which involves the central nervous system and the meninges. The symptoms depend upon the extent of the involvement. This disease may occur either epidemically or sporadically. The malady is endemic in America, and epidemics occur in the late summer. The *morbidity and mortality rates* increase progressively with each decade of life. No age is exempt. The highest incidence is in individuals more than twenty-five years of age. The *incubation period* has been estimated to range from four to twenty-one days.

CLINICAL PICTURE.—As in the other encephalitides, the cases vary from mild or abortive cases, which exhibit only headache



and fever, to those with an abrupt onset, characterized by high fever, nausea, vomiting, vertigo, headache, nuchal rigidity, Kernig's sign, mental confusion and tremor. Paralysis is not a common finding in these cases and involvement of the ocular muscles is extremely rare. Spinal fluid is usually under increased pressure, but is free from any ordinary bacteria, either by smear or culture, the sugar is not diminished and may be increased or normal, globulin is increased and the total cell count is increased, the increase usually consisting chiefly of lymphocytes. Those who recover from this disease usually do so quickly, the temperature falling by lysis and reaching a normal level in five to ten days. In exceptional cases it may persist for three to six weeks. Those who recover are not usually bothered by troublesome or disastrous sequelae.

**DIAGNOSIS**—Diagnosis depends upon the isolation of the virus from brain tissue (as blood, spinal fluid and nasal washings are not infective), or by showing the development of neutralizing and complement fixing antibodies during convalescence. It has been shown where epidemics have been prevalent that 50 per cent or more of the normal population may have antibodies to St. Louis encephalitis virus. A single convalescent specimen is of no value in making a positive diagnosis, although it is of considerable significance if it is negative. For this reason it is necessary to have a specimen of serum taken when the patient is first ill, two weeks thereafter and at six weeks. In this way an increase in the titer of the neutralizing antibodies or the complement can be demonstrated showing the recent infection by the virus in question.

*Transmission* of this disease is by mosquito vector. Droplet infection transmission from man to man has never been proved. The *natural reservoir* for this disease is mammals and birds and possibly human carriers.

**TREATMENT**—The treatment, as outlined previously for Encephalitis Lethargica, is symptomatic as there is no specific vaccine, drug or serum which is of value. The spinal fluid pressure should be kept within the limits of normal by repeated lumbar punctures, and the intravenous injection of hypertonic glucose solution may relieve the headache. Fluid intake should be freely maintained and if necessary the patient should be fed by gastric tube.

**PROPHYLAXIS**—There is no efficient vaccine available at the present time

#### EASTERN EQUINE ENCEPHALITIS

Eastern equine encephalitis is an epidemic disease of the late summer. The majority of reported cases have occurred in children under ten years of age. The *mortality rate* in recognized cases has been approximately 60 per cent.

**CLINICAL PICTURE**—The onset of the disease is usually sudden, particularly in the younger children, with the temperature rising rapidly to 103° to 105° F. Convulsions occur during the course of the disease. Coma may develop rapidly and persist throughout the acute stage of the illness. There is nuchal rigidity, positive Kernig's sign, stiffness of the back, and sometimes in the younger patients a peculiar edema of the face and upper extremities. Eye signs have been common and ocular motor palsies are present. Early in the illness there is a leukocytosis. The spinal fluid is under increased pressure and its total cell count is increased, averaging approximately 2000 per cubic millimeter. Early in the illness the majority of these cells are polymorphonuclear leukocytes, however, later in the illness there is a predominance of lymphocytes. In the patients who recover the temperature returns to normal by lysis, usually six to ten days after the onset.

In the reported cases eastern equine encephalitis differs from western equine encephalomyelitis and St. Louis encephalitis in that a large percentage of those who survive it have severe mental or physical damage.

**DIAGNOSIS**—Diagnosis in man depends upon the development of specific neutralizing and complement fixing antibodies or the isolation of the virus from the brain. It is believed that the blood and spinal fluid are infective before the onset of the neurological signs and symptoms. The *natural reservoir* for this disease is birds and mammals and the vector is most probably a mosquito.

**PROPHYLAXIS**—As this disease may reach epidemic proportions and the vector is the mosquito, mosquito control must be considered. In horses, formalized chick embryo vaccines have been successfully used.

**TREATMENT**—There is no specific therapy and the treatment is entirely symptomatic. (See Treatment under Encephalitis Lethargica.)

## WESTERN EQUINE ENCEPHALOMYELITIS

Western equine encephalomyelitis is epidemic in the late summer. This disease is usually a milder variety of the same clinical picture as eastern equine encephalitis, but it has occurred mainly in adults, a large proportion of whom have been male agricultural workers. The *mortality rate* for this age group is approximately 5 per cent. In infancy and in old age the mortality rate is higher.

**CLINICAL PICTURE**—Clinically, the diseases caused by St. Louis virus and western equine encephalomyelitis virus are so similar that it is impossible to differentiate them clinically. *In infants* the infection is usually of a sudden onset, with fever, refusal to eat followed by vomiting, rigidity of the neck, twitching and occasionally convulsions. The temperature rises to 103° to 105° F and remains at that high level for twenty-four to forty-eight hours. In most cases the temperature falls to normal in the next three or four days. Cyanosis may be conspicuous during the acute illness. The child may completely recover in from four or five days to a week after the onset of the illness. It is extremely important in treating these children that repeated lumbar punctures be done to keep the spinal fluid pressure at approximately normal level. This greatly reduces the number of cases with permanent residual damage.

*In adults* the disease is very similar to eastern equine encephalitis. The clinical picture, however, is usually milder and recovery usually takes place within two or three weeks. The spinal fluid is usually under increased pressure with cell count varying between 15 and 500 cells. During the first days of the illness there may be an increase of polymorphonuclear cells up to or more than 50 per cent, but later the lymphocytes predominate. Here also it is believed that the spinal fluid and blood are infected before the onset of neurological symptoms and signs, but in order to make a diagnosis it is necessary to isolate the virus from the brain or to demonstrate the development of neutralizing or complement fixing antibodies in the convalescent serum. The *natural reservoir* is thought to be birds and mammals and the vector is probably the mosquito.

**PROPHYLAXIS**—Formalized chick embryo vaccine has been used, and anyone who by reason of his work must be heavily exposed to mosquito bites in an endemic area should be offered

the probable protection afforded by this vaccine. There seems to be no reason for hesitating to vaccinate those who request it. It is recommended that 1 cc be given subcutaneously in each of two doses at weekly intervals, and that the patient be observed for one hour after vaccination, adrenalin being kept immediately available to combat any anaphylactic type of reaction.

Mosquito control for the community should also be stressed. Because of the number of known viruses that are transmitted by the mosquito and the great likelihood of the existence of others which so far have not been isolated, it might be reasonable to emphasize mosquito control as a general prophylactic measure and one especially appropriate in this disease, where the morbidity rate is so low.

#### JAPANESE ENCEPHALITIS

In Japan there have been two varieties, type A and type B. Type A seems to be the same as Von Economo's encephalitis. Type B resembles very closely St. Louis encephalitis, but there are some serologic differences between their viruses. The average *mortality rate* is approximately 65 per cent. Spinal fluid cell increase is chiefly in lymphocytes. Neurological residuals are infrequent. *Diagnosis* in men is dependent upon isolation of the virus from the blood, rarely is it ever found in the spinal fluid or the brain. The development of neutralizing and complement fixing antibodies in the sera of convalescent patients is of diagnostic aid. *Transmission* is believed to be by the mosquito vector, probably the *Culex*. There is no conclusive proof that the disease can be transmitted by droplet infection from man to man. *The natural reservoir* is believed to be horses and, questionably, human beings. Clinically this encephalitis is indistinct from St. Louis encephalitis.

**PROPHYLAXIS.**—There is no efficient vaccine available at the present time and mosquito control must be considered.

#### RUSSIAN ENCEPHALITIS

Russian encephalitis is endemic in the late spring and early summer. It is also called verno-aestival or tick-borne encephalitis, and most frequently affects males, principally forest workers. The *mortality rate* is given at approximately 30 per cent. Spinal fluid pressure is increased and the cell count varies from ap-

proximately 25 to 150 cells, these are chiefly lymphocytes. In 20 per cent of the cases there is some residual atrophy, and paralysis of the neck and shoulder girdles is present. The disease in man is *transmitted* by ticks and the *natural reservoir* is said to be wild rodents and ticks. *Diagnosis* in man depends upon the isolation of the virus from the blood, spinal fluid and brain and the development of neutralizing antibodies.

**PROPHYLAXIS**—Personal prophylaxis against ticks and active immunity with a formalized mouse-brain vaccine have been used. *Treatment* of this disease is symptomatic.

### RABIES

(Lyssa or Hydrophobia)

Rabies is widely distributed in mammals and has been transmitted to man by dogs, cats, cattle, horses, sheep, swine, wolf, fox, skunk, squirrel, raccoon, vampire bat and rat. Although rabies is usually passed from some recognized case it may occur from an unknown origin. A definite instance of rabies in animals and man in the West Indies and South America has followed the bite of an apparently healthy vampire bat. Rabies virus may lurk in unsuspected skunks and foxes in their natural habitat before giving rise to an epizootic. Other animal species not yet implicated may also harbor the virus and thus constitute additional unknown sources of infection. Despite these possibilities, rabies, as known in this country, rises mainly not from healthy carriers but from animals in some stage of the disease. The dog is involved nine times more often than all other animals combined.

The rabies virus rarely penetrates the intact body surface. Usually there must be a wound and a sufficient amount of virus present before infection can take place. The virus passes from the site of the bite along the nerve to the central nervous system. Once the virus has gained a foothold in the spinal cord or brain, the animal or patient is doomed. The percentage *mortality* from rabies following the bite of a presumably rabid dog ranges from 2 per cent to more than 50 per cent.

**DIAGNOSIS**—Diagnosis depends upon the demonstration of Negri bodies in certain nerve cells, especially in the pyramidal and ganglion types in Ammon's horn. The final and most conclusive test for rabies is the inoculation of mice for the isolation and identification of the virus from Ammon's horn tissues.

Webster has developed and described a mouse inoculation test for the diagnosis of rabies

**RABIES IN THE DOG**—If a dog is suspected of having been exposed to rabies, it should be isolated for a period as long as three months. If it is well after two months it may be released with the knowledge that only rarely does the animal develop rabies after this time. If the animal becomes ill it should be carefully observed until it dies or becomes prostrate. Then it should be killed and the Negri body test should be performed on the brain tissue. If both clinical disease and the Negri bodies are typical, the mouse test may be regarded as superfluous. If the animal does not develop typical rabies, a qualified person must take the responsibility of deciding whether the disease is sufficiently suggestive of rabies to kill the animal. In this case the mouse inoculation test becomes imperative and yields a result which is reliable. If the test is positive, the rabies virus was present in the brain, whether or not the animal appeared sick or had Negri bodies. If the mouse test is negative, the animal did not have rabies. When a questionable dog is killed or found dead, its brain should be examined for Negri bodies and also the mouse inoculation test should be performed. The mouse test should be used in all doubtful cases.

**RABIES IN MAN**—Once the disease develops in a human the patient is doomed, consequently all treatment must be symptomatic. The patient is to be kept as quiet as possible in a darkened room. Chloroform and morphine may be used for sedation. Occasionally the application of cocaine to the throat will allow the patient to take liquid nourishment. If the patient is unable to swallow readily, fluid should be given parenterally.

**PROPHYLAXIS**—By the muzzling of dogs the disease can be greatly reduced. Although preventive vaccination of dogs has been done, it has been unsatisfactory. If an individual is bitten by a suspected animal, bleeding should be encouraged and the wound opened and washed with bichloride of mercury 1:1,000 solution. It has been recommended that fuming nitric acid be applied to the bite. If this is done, vaseline should be applied around the wound to avoid burning the surrounding tissues, and the acid applied drop by drop. A pipette or glass rod may be used for this purpose. The worth of fuming nitric acid has not been proved and it seems very likely, as McMaster and Hudack

have shown, that the lymphatics quickly pick and carry away any particles that are introduced into an open wound. Therefore, when the face is involved, especially in women, it is questionable whether the acid should be used at all.

*Vaccine* prophylaxis consists of daily injections of rabies vaccine for at least fourteen days. The vaccine, usually 2 cc., is injected subcutaneously following sterile precautions, a quadrant of the abdomen is used each day and each injection is separated as far as possible from the previous site. During treatment the individual is permitted to lead a normal life but is advised to avoid unusual exercise. The dose is the same for persons of all ages, but it is always increased in quantity or number in cases of severe bites. Webster recommends vaccine treatment in the following circumstances: "(1) Persons bitten through the skin by animals proved rabid, (2) persons bitten through the skin by animals which cannot be proved nonrabid, (3) persons without bite but in intimate contact with rabid dog, moistened by saliva, etc., and (4) persons without bite but in intimate contact with possibly rabid dogs." Many authorities advise against treatment of persons not bitten or scratched through the skin except in the case of children who have had an intimate contact with a dog known to be rabid.

#### WEST NILE FEVER

This virus was isolated from the blood of natives with a febrile illness in Uganda. It is immunologically related to the viruses of St. Louis and Japanese encephalitis. Little is known of the clinical diseases it produces. It seems to be widespread throughout Central Africa.

#### ASCENDING MYELITIS

This or the so-called Landry's type is an ascending paralysis which may be caused by several agents. It is the common experience that the etiologic agent cannot be isolated in all of these cases. The occasional finding of rabies virus in patients with this disease was mentioned before. Furthermore, in young adults poliomyelitis may present a picture corresponding to the Landry's paralysis. Acute infectious polyneuritis (infectious neuritis), manifests itself in the Landry's type of paralysis more

often than in other diseases. There is no definite evidence that polyneuritis is a virus disease.

#### POSTINFECTIOUS HEMORRHAGIC ENCEPHALITIDES

These encephalopathies may occur following measles, mumps, influenza, varicella, or vaccina, after rabies treatment, following arsphenamine therapy, or without any known previous infection. In both types of disease, demyelinating lesions are found on histological section and these are pathognomonic. The distribution of the demyelination varies somewhat in the two encephalopathies, as does the amount of hemorrhage. The etiology of these cases is not understood, and there is little reason at the present time to believe that a viral agent is involved.

#### LYMPHOCYTIC CHORIOMENINGITIS

This disease is also called acute aseptic meningitis. It is endemic in character and the symptoms are essentially those of acute meningitis. Headache is a very prominent symptom. Epidemics have not been encountered in man. The virus attacks not only the nervous system, but may cause an influenza-like picture or an acute leukemia-like picture. The *mortality rate* is low. *Transmission* may be by contact with the virus in the droppings and urine of infected house mice.

*Diagnosis* in man depends upon the symptoms and signs of acute meningo-encephalitis with findings of an increased spinal fluid pressure and increased spinal fluid cell count. Lymphocytes predominate, and may vary from 200 to 2000 cells per cubic millimeter. No organisms are seen on stained smears and the spinal fluid shows a normal glucose content with normal or high protein. Diagnosis finally rests upon isolation of the virus from the blood, spinal fluid, spleen or brain and the development of neutralizing antibodies and complement-fixing antibodies. The *natural reservoir* for this disease is house mice and, questionably, dogs.

**PROPHYLAXIS**—The exclusion of mice from the living quarters and storage of food supplies to prevent contamination with mouse droppings or urine are the only known means of prophylaxis.

**TREATMENT**—This is entirely symptomatic.



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## PEDIATRIC EMERGENCIES\*

CHARLES C CHAPPLE, MD†

THE purpose of this symposium is to bring to those carrying the heavy burden of professional service at home a better understanding of the conditions with which, perhaps, they have had but limited recent experience, but for which they are now called upon to give adequate treatment. Therefore it is the intention to cover in this brief synopsis the differential diagnosis and treatment of certain common conditions which, ordinarily, might or might not be considered pediatric emergencies.

### PREMATURITY

The prematurely born infant, to accept a common definition, includes all infants under 5½ pounds in weight. As the primary consideration in its care, extra warmth must be supplied such an infant unless the room temperature is 85° F or more. High humidity also is desirable. Care must be taken that the heat surrounding the infant is not too great, or his body temperature will climb above normal. Heat can be supplied best by an incubator. These devices vary in complexity, but for home use simple models are available. Their specifications can be obtained from the Children's Bureau, Department of Labor, Washington, D C. The premature infant is particularly susceptible to infections, therefore the nurse must wear a mask besides taking the usual care in scrubbing.

The premature infant can tolerate as high a caloric intake per pound of body weight as a normal baby. Breast milk is the most desirable food, but evaporated milk and sugar can be substituted when breast milk is not available. The proportion will be discussed in a later paragraph on feeding. The feeding schedule for a small infant must have shorter intervals between nursings than

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\* From the Department of Pediatrics, School of Medicine, University of Pennsylvania, and the Children's Hospital of Philadelphia.

† Associate in Pediatrics, School of Medicine, University of Pennsylvania, Associate Pediatrician, Hospital of the University of Pennsylvania and the Children's Hospital of Philadelphia.

for a full term baby. For a very small infant it is sometimes necessary to give the feedings as frequently as every two hours. When practicable it is not unwise to feed him whenever he cries, thus giving frequent small feedings.

Vitamin K is of particular importance to the premature infant and should be given immediately after his birth. Vitamin C is the most important of the vitamins to be fed the baby regularly. The premature infant requires twice the amount of this vitamin that suffices the normal infant so he should be given 100 mg per day as early as he is able to take it. Vitamins A and D should be added to the dietary by the time the infant is ten days old. These are best given in a cod liver oil concentrate and started at one drop, increasing one drop daily until an adequate intake is reached. This quantity should approximate that required by a normal full term infant. Vitamin B, also in concentrated form, should be started with one drop when the optimum of A and D is reached. Iron, despite the physiological anemia, should be avoided in infants under 5 pounds as they are unable to assimilate it. At that weight, however, it should be started in a liquid form as in Elixir Feosol, beginning with one drop a day and increasing until an adequate quantity is given, or the appearance of black in the infant's stool shows that it is not all being utilized. Occasionally, too, iron will cause a loss of appetite in which case it should be reduced to an amount which does not produce symptoms.

#### CARE AND FEEDING OF THE NORMAL INFANT

Before proceeding to a discussion of abnormalities it might be wise to mention a few facts concerning the normal infant. He can see, hear, and has his other senses at birth though for his first four months he utilizes them but little. Until that time he is largely unaware of the outside world. He cries only when he is hungry, wet, or otherwise uncomfortable. He may have ten or more small stools a day, or, especially when breast fed, he may have one every third or fourth day only. He may regurgitate a little after feedings or even vomit occasionally, when he has been handled more than usual. He probably will require a feeding every fourth hour, but if he is small he may demand it more frequently. One cannot be arbitrary about the schedule though regularity is desirable. Until the infant weighs 9 pounds

he usually needs a 2 A M nursing If he sleeps through the night there is no need to insist upon this in a well baby At five months of age he probably will be willing to drop the 10 P M feeding, and at a year he will go on three meals a day.

Breast feeding is the most desirable feeding for all infants It does not disagree with more than one in a hundred, and it seldom if ever needs milk analysis When breast milk is not available a thoroughly reliable clean, uniform formula can be made of evaporated milk and sugar The infant's tolerance to evaporated milk is greater than to other forms of cows' milk because of the duration of the heating it has undergone When evaporated milk causes digestive symptoms, pasteurized goats' milk, or certain synthesized proprietaries should be substituted since the difficulty is almost certain to be due to milk allergy.

An infant's requirements are covered by 50 calories and approximately  $2\frac{1}{2}$  ounces of fluid per pound of body weight. The calculations of proper formulas are simple Of the required calories, two thirds should be supplied by the milk which is 40 calories per ounce (if evaporated milk is used) and one third by the sugar which is 120 calories per ounce Boiled water is added in a sufficient quantity to meet the fluid requirements The minimum quantity of water to be added to a large can of evaporated milk ( $13\frac{1}{2}$  ounces by volume) is 17 ounces If the formula is to be made of pasteurized milk (20 calories per ounce), the milk should be boiled hard for three minutes and the "skin" which has formed on cooling removed Raw unboiled milk has no place in any dietary, but it can be made safe by boiling The choice of sugars includes syrups of which Karo is an example, honey, granulated sugar, and proprietaries Ordinarily the choice between them is one of flavor or some other practical consideration At three to four months, vegetables may be given at the third meal Liver soup preparations are a good meat source for the infant, and may be added to the vegetables when he is taking the latter well It is wise to allow at least a week between the additions of new foods Egg may be started safely at seven to eight months and is given on alternate days with the meat Fruits and desserts are added at eight to ten months Vitamins should be added as recommended under the paragraphs on prematurity, and iron is a good adjunct for most infants

## EXAMINATIONS

Examinations of infants should include orthopedic inspection. The normal infant has a physiological flat foot and should not be put into orthopedic shoes. Such shoes should be prescribed only for children whose difficulty in walking warrants them, but not prescribed routinely. The normal infant should be able, when lying on his back with thighs flexed on the abdomen and legs flexed on the thighs, to abduct his knees almost to the point touching the examining table. When abduction is possible only 45 or 50 degrees from the perpendicular, x-ray examination of the hips should be done as a precautionary measure for congenital dislocation of the hip. Under three months of age this may be the only sign present of this condition but at this age shortening, as well, becomes evident and is demonstrated by the asymmetry of the gluteal knee and ankle folds.

## IMMUNIZATIONS

Vaccination for smallpox may be given at any time after birth, preferably before seven months of age since reactions during early infancy are not severe. Inoculations of whooping cough vaccine containing 10 to 20 million killed bacilli per cubic centimeter should be administered to a total of 7 cc. in three inoculations divided 1 cc. in each arm or leg on the first occasion, and 1.5 cc. in each at a different site on the second and third. For diphtheria prevention, alum-precipitated toxoid, 0.5 or 1 cc. depending upon its strength, should be given monthly for three doses. Tetanus toxoid may be combined with the diphtheria toxoid and given in the same inoculation. While tetanus prevention is not entirely dependable as complete protection from infection developing in a severe wound later in life, it obviates the necessity of giving the tetanus antitoxin for every minor injury. Instead, a further dose of the toxoid should be given in the event of a wound requiring tetanus protection, except when the wound is severe enough to warrant giving both toxoid and antitoxin.

All the specific immunizations should be completed before the child is one year old, although they are not contraindicated thereafter. Scarlet fever inoculations are of questionable value. Measles and mumps have no specific preventives except for the transient passive immunities (of two to three weeks) following

any of the injections mentioned subsequently under the specific diseases.

In the discussion of abnormalities which follows, an attempt will be made to group the conditions according to systems and to consider them as chronologically as possible

### GASTRO-INTESTINAL DISORDERS

*Constipation* seldom requires serious consideration. The cause is usually dietary, although it can be caused by atony or spasticity of the large intestine and the diagnosis established by large, soft, stools, or by small, rabbit-like, hard stools. An increase in the carbohydrate content of the formula or a change to a less refined sugar will frequently relieve it. Prune juice and milk of magnesia are useful adjuncts. Castor oil seldom, if ever, should be used.

*Colic* is pain and as such is a symptom, not an entity. Its most frequent cause is underfeeding, but gastro-intestinal disturbances may cause it. An additional feeding will usually relieve the distress but an enema should be given if the taking of food does not stop the attack immediately. A thorough examination for other causes of pain should be made.

*Intussusception* begins as an attack of colic which is promptly accompanied by projectile vomiting and all the symptoms of acute intestinal obstruction, including shock. An enema, given immediately after the onset, with the enema bag held 3 to 5 feet above the infant and the patient's buttocks held tight together in order to retain the water, will frequently overcome the beginning intestinal invagination. Once invagination is established an enema will reveal mucus and blood, and immediate operation is the only course to be chosen.

*Pyloric stenosis* and *pylorospasm* are to be suspected in the presence of continual projectile vomiting in early infancy. Although the former usually appears in boys and the latter in girls, this is not always the case. Visible peristalsis, after feedings, may be demonstrable in either condition. Constipation and infrequent urination follow as a result of the small quantities of food retained. All symptoms are likely to reach their peak at six weeks of age. Pylorospasm can be relieved by atropine which is most easily given as tincture of belladonna, 1 minim in a teaspoonful of water fifteen minutes before feedings. This dose

can be increased 1 drop at a time until flushing of the face is produced and then reduced to the maximum safe level. Atropine may be continued regularly as long as necessary. Pyloric stenosis requires operation, but a diagnostic trial of atropine and thickened feedings, made by the addition of 5 to 10 per cent cereal to the formula, should be given first.

*Appendicitis* occurs frequently throughout childhood. Its signs are the same as in the adult. Rectal examination is invaluable as a diagnostic measure.

*Teething* frequently causes symptoms which include swollen gums and fever. Additionally, it lowers the resistance of the infant to a point where he becomes susceptible to minor infections. Incision of the gum over the tooth is indicated rarely but is at times helpful.

*Gingivitis* yields to gentian violet, 1 per cent aqueous solution, and (in older children) to mouth washes of hydrogen peroxide and zephiran. In very severe cases the application of a direct stream of oxygen for prolonged periods is of benefit in preventing noma.

### RESPIRATORY TRACT DISEASES

*Colds* are of no more serious import in otherwise healthy infants than in older children. Suction of mucus from the nares of infants can be accomplished with an ordinary bulb syringe. This procedure, done frequently by the mother, adds greatly to the baby's comfort.

*Tonsillitis* is a self-limited disease usually causing a high temperature for two or three days. Otitis media may complicate it, but treatment for the tonsillitis itself is usually limited to small doses of aspirin given occasionally to control the fever.

*Otitis media* is a common complication of colds and of teething. Treatment should be directed toward the opening of the eustachian tube by means of astringent drops such as 0.5 per cent ephedrine hydrochloride instilled into the nose when the baby is lying flat on its back. Additionally, heat, preferably in the form of light, should be applied to the ear itself. An efficient, simple heater can be made by cutting the bottom of a round can or container so that it will fit around the socket on an extension cord. The smallest bulb available should then be screwed into the socket through the open end of the can. This



any of the injections mentioned subsequently under the specific diseases

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*Constipation* seldom requires serious consideration. The cause is usually dietary, although it can be caused by atony or spasticity of the large intestine and the diagnosis established by large, soft, stools, or by small, rabbit-like, hard stools. An increase in the carbohydrate content of the formula or a change to a less refined sugar will frequently relieve it. Prune juice and milk of magnesia are useful adjuncts. Castor oil seldom, if ever, should be used.

*Colic* is pain and as such is a symptom, not an entity. Its most frequent cause is underfeeding, but gastro-intestinal disturbances may cause it. An additional feeding will usually relieve the distress but an enema should be given if the taking of food does not stop the attack immediately. A thorough examination for other causes of pain should be made.

*Intussusception* begins as an attack of colic which is promptly accompanied by projectile vomiting and all the symptoms of acute intestinal obstruction, including shock. An enema, given immediately after the onset, with the enema bag held 3 to 5 feet above the infant and the patient's buttocks held tight together in order to retain the water, will frequently overcome the beginning intestinal invagination. Once invagination is established an enema will reveal mucus and blood, and immediate operation is the only course to be chosen.

*Pyloric stenosis* and *pylorospasm* are to be suspected in the presence of continual projectile vomiting in early infancy. Although the former usually appears in boys and the latter in girls, this is not always the case. Visible peristalsis, after feedings, may be demonstrable in either condition. Constipation and infrequent urination follow as a result of the small quantities of food retained. All symptoms are likely to reach their peak at six weeks of age. Pylorospasm can be relieved by atropine which is most easily given as tincture of belladonna, 1 minim in a teaspoonful of water fifteen minutes before feedings. This dose

can be increased a drop at a time until flushing of the face is produced and then reduced to the maximum safe level. Atropine may be continued regularly as long as necessary. Pyloric stenosis requires operation, but a diagnostic trial of atropine and thickened feedings, made by the addition of 5 to 10 per cent cereal to the formula, should be given first.

*Appendicitis* occurs frequently throughout childhood. Its signs are the same as in the adult. Rectal examination is invaluable as a diagnostic measure.

*Teething* frequently causes symptoms which include swollen gums and fever. Additionally, it lowers the resistance of the infant to a point where he becomes susceptible to minor infections. Incision of the gum over the tooth is indicated rarely but is at times helpful.

*Gingivitis* yields to gentian violet, 1 per cent aqueous solution, and (in older children) to mouth washes of hydrogen peroxide and zephiran. In very severe cases the application of a direct stream of oxygen for prolonged periods is of benefit in preventing noma.

#### RESPIRATORY TRACT DISEASES

*Colds* are of no more serious import in otherwise healthy infants than in older children. Suction of mucus from the nares of infants can be accomplished with an ordinary bulb syringe. This procedure, done frequently by the mother, adds greatly to the baby's comfort.

*Tonsillitis* is a self-limited disease usually causing a high temperature for two or three days. *Otitis media* may complicate it, but treatment for the tonsillitis itself is usually limited to small doses of aspirin given occasionally to control the fever.

*Otitis media* is a common complication of colds and of teething. Treatment should be directed toward the opening of the eustachian tube by means of astringent drops such as 0.5 per cent ephedrine hydrochloride instilled into the nose when the baby is lying flat on its back. Additionally, heat, preferably in the form of light, should be applied to the ear itself. An efficient, simple heater can be made by cutting the bottom of a round can or container so that it will fit around the socket on an extension cord. The smallest bulb available should then be screwed into the socket through the open end of the can. This

simple reflector can direct the light and heat into the ear and be applied safely as long and frequently as is required for the relief of pain. In infants, care must be taken that too great heat is not developed. Such a heater can be used not only for the pain of the acute ear, but also to shorten the course of a draining ear. The sulfonamides should be considered if the condition warrants it, and with these, low dosage ordinarily suffices.

*Croup* is a laryngitis with sufficient edema and spasm to cause obstructive dyspnea. It yields to steam inhalations and the use of an expectorant. The onset of croup as a rule, is sudden. A child with a barking cough suddenly has difficulty in breathing. When this occurs the child should be taken into the bathroom where hot water can be run into a tub to produce a steamy atmosphere. Syrup of ipecac, 5 minims, should be given directly onto the tongue at intervals of one-half hour or less if the symptoms persist, or until vomiting is produced.

*Pneumonia* in childhood may be difficult to detect in the first two days after its onset. However, if there is a high fever, a respiratory rate greater than 40 per minute, and a cough, it is a reasonably sure presumptive diagnosis, although physical signs will reveal only a moderate suppression of breath sounds over the involved area which may be small. Sulfathiazole or sulfadiazine should be given in dosages up to  $1\frac{1}{2}$  grains per pound of body weight in twenty-four hours. When sulfadiazine, particularly, is used, one-half the dose for twenty-four hours can be given initially. Sulfonamides in general are better tolerated when soda bicarbonate is given simultaneously in approximately the same dosage. It is important when giving sulfonamides to be certain that an adequate urinary output is maintained.

Atypical or so-called "*virus*" *pneumonia* at this time appears to include in a group of protracted pneumonias all those which are sulfonamide resistant. Specific therapy beyond the use of convalescent serum is unavailable.

#### GENITO-URINARY DISORDERS

*Pyelitis* is much more common in girls than in boys. Daily temperature rises as high as  $104^{\circ}$  F are usual. In the first few days of fever, white cells may not appear in the urine, but the diagnosis cannot be definitely established until they do. Ideally a catheterized specimen is examined. Fluids and alkalies, especially sodium citrate, are ordinarily sufficient treatment. More

severe cases require alternation between alkali and acid-producing medications. One of the sulfonamides may be indicated. A prolonged course, or frequently repeated attacks, warrants a thorough examination of the genito-urinary tract.

Boys occasionally have an infection in the presence of phimosis which at first resembles a nonspecific urethritis, but which in reality is limited to the external surface of the glans. Frequent bathing of the glans with a mild antiseptic solution, followed by hydrogen peroxide, will check the process.

*Gonorrheal vaginitis* is a local infection in girls before puberty which does not spread to the fallopian tubes. The use of the estrogenic hormone, when possible in the form of vaginal suppositories, is indicated. Additionally, sulfadiazine should be given by mouth.

#### EXANTHEMS

*Roscola infantum* is a mildly infectious disease occurring in infants under three years of age. A fever, usually accompanied by a mildly red throat, is the only sign present until, on the fifth day, a mottled, nondescript rash appears. With its appearance the child recovers. The disease requires no treatment beyond aspirin to control the temperature.

*Measles* may occur at any time after six months of age. Its incubation period is from ten days to two weeks. Coryza, the first symptom, soon develops into photophobia accompanied by a severe cough. If Koplik spots are present they confirm the diagnosis, but they do not always appear. These are white, sand-like spots with a small red areola around them on the gums near the buccal margin. The rash which usually follows the Koplik spots by one to two days and onset of the coryza by three to four days, begins about the lobe of the ear and the upper part of the neck and the lower part of the face, spreading rapidly to the rest of the body, and is composed of coppery red spots, which vary from the size of a split pea to that of a quarter, with areas of normal skin between them. Treatment is nonspecific and consists of keeping the patient in a darkened room as long as light hurts his eyes, aspirin and other coal tar derivatives to assist in his comfort, and cough mixtures. Complications are usually limited to otitis media, but may include pneumonia. During the course of severe measles, rales can be heard throughout the chest regularly.

Measles from a known exposure can be prevented or modified to allow the production of active immunity without suffering a severe attack. Such prevention or modification is achieved by the administration of intramuscular blood from a person who has had the disease in childhood, pooled adult serum, placental extract, or gamma globulin obtained from plasma fractionation by the method of Cohn. When blood is to be given, it need not be matched since it is injected intramuscularly. Inoculation should be given before the fifth day after exposure. Active immunity by means of an attenuated measles virus is being tested experimentally but vaccines of this type are not as yet available.

*Scarlet fever* has an incubation period of forty-eight hours to ten days. Its onset is frequently accompanied by vomiting. An edematous, red throat and heavily coated tongue bordered in bright red are always present when the disease is established. The rash is a blush with a goose-flesh appearance. This is evident behind the ears, on the flexor surfaces, and most strikingly on the lower abdomen. It avoids the region about the mouth, which consequently looks pale. Complications, though not common, are severe and include cardiac and renal involvement. Prevention following a known exposure can be accomplished by the administration of convalescent serum, which is also of value in treatment. Sulfanilamide or sulfadiazine may be used to advantage.

*Chickenpox* is a mild disease which has rare complications and needs treatment only for the itchiness (calamine lotion) and rarely to prevent secondary infection of the vesicles. Its incubation period is approximately two weeks. At the end of this time the vesicles, filled with clear fluid, appear on the trunk. For five days they increase in number during which time the earlier ones have become purulent. These lesions occur largely on the covered areas of the body, although occasional ones occur on the hands, feet and face.

*Smallpox* resembles chickenpox, but the lesions occur in greater numbers on the exposed parts, and frequently become confluent. Absence of recent vaccination, history of exposure, the uniform lesions not appearing in the crops which are characteristic of chickenpox, and a much more severe course, are the distinguishing factors between this disease and chickenpox.

## OTHER COMMUNICABLE DISEASES

*Mumps* occurs at any time after the second year of life. Before adolescence it is almost free of complications. Treatment is limited to ice packs locally and aspirin. After puberty orchitis is very common. Convalescent serum is of questionable value in treatment but may have value as a preventive measure. It certainly has much less striking effects than specific convalescent sera in the prevention of measles and scarlet fever. Orchiotomy, incision of the tunica albuginea, by releasing the pressure caused by the orchitis, offers promise in the prevention of testicular atrophy.

*Whooping cough* occurs at any age. The cough, which is usually worse at night, is characterized by an increasing number of coughs between inspirations, and is frequently followed by vomiting. Diagnosis usually can be established bacteriologically in the early days of the disease, and by the end of the third week by the appearance of a lymphocytosis. Treatment consists of expectorants to thin the ropy mucus. Diet should consist of small frequent feedings. Cough mixtures and sedatives are of little value. X-ray treatments of the trachea occasionally help. In infants under one year, in whom the mortality is very high, hyperimmune convalescent serum as treatment has produced excellent results. Preventive inoculations should be given all infants routinely.

*Diphtheria* is a disease which should not be encountered except in very young infants who have not yet received preventive inoculations. It is characterized by a gray adherent membrane on the pharynx, bloody serous discharge from the nose, or increasing obstructive dyspnea. Diagnosis must be corroborated bacteriologically. Treatment is accomplished by antitoxin.

*Meningitis* can be caused by many different organisms. The symptoms in all cases, however, are similar. Stiff neck, increased or decreased knee jerks, headache, fever, are common to all. Brudzinski's sign is a reliable indication of early meningeal involvement. A spinal tap, followed by a complete examination of the fluid obtained, is necessary for corroboration of the diagnosis. Meningococcus meningitis responds well to sulfonamide therapy. Other types may or may not respond, depending upon the causative organism. However, many cases of the previously fatal influenzal meningitis have now recovered under this treat-

ment. Serum and symptomatic measures may be required as well

*Anterior poliomyelitis* has no known preventive. It is recognized by the occurrence of meningeal signs following a normal interval of several days after a preliminary low fever. A gastro-intestinal disturbance or symptoms of an upper respiratory tract infection may have been present during the first low fever. The meningeal signs are usually accompanied by pain and tenderness of the extremities and elsewhere. Its transmission may be by one of several routes—contaminated food or water, inhalation of the virus, direct contact and insect bites. The treatment which appears the most promising is the Sister Kenny regimen and possibly in addition the cautious use of prostigmine.

#### MISCELLANEOUS

*Convulsions* are symptoms. They may occur at the onset of any disease in childhood. Frequently temperatures of 105° F and above will produce them. Treatment should deal with the reduction of the temperature by means of ice packs to the head, cooling sponges or baths, and the diagnosis of the underlying pathology. In the absence of high fever, hypoglycemia is a possible cause. In early infancy, tetany of hypocalcemic origin must be considered. As treatment, saline and 5 per cent glucose infusions are of value in either case. Determinations of the blood levels of calcium and of blood sugar will be necessary to distinguish them. Dietary adjustment, with emphasis on an increase of protein content, should prevent wide blood sugar fluctuations. Calcium gluconate intramuscularly, for the acute phase, to be followed immediately and continuously by large doses of vitamin D, should prevent the recurrence of convulsions from tetany. Allergies and gastro-intestinal disturbances sometimes cause convulsions.

*Meningismus* is a rigidity of the neck sometimes associated with increased knee jerks and is a symptom, not an entity. It may be present as a complication of pyelitis, adenitis, and other infections. The spinal fluid may have an increased number of cells and be under increased pressure. Negative bacteriological examination of this fluid and the determination of an underlying cause are necessary to establish the diagnosis. Treatment is directed toward the underlying condition.

# THE RECOGNITION AND MANAGEMENT OF CARDIAC EMERGENCIES

REYNOLD S GRIFFITH M.D.\*

IN consideration of the title of this clinic, the question naturally arises, what is a cardiac emergency? Actually, any acute or chronic cardiovascular disease manifesting symptoms of acute cardiac distress may be included in this classification. Space would not permit such a general consideration so by necessity this discussion will be limited to those emergencies which are most commonly encountered.

A definite increase in the incidence of cardiovascular disease may be expected both in the civil population and military personnel either directly or indirectly as a result of the war. Acute infectious diseases, malnutrition, nervous and physical strain, are important contributing factors. Such conditions not only are conducive to the development of cardiovascular degeneration but predispose to acute exacerbation of pre-existing diseases. Already an increase in acute cardiac accidents has been reported from several war plants, especially in the older age groups which have been called back from retirement or sedentary activities. Those with previous vascular and myocardial degeneration manifest evidence of failure either by a gradually progressing myocardial weakness or by an acute collapse. The most common accidents are a result of coronary artery disease such as angina pectoris or coronary occlusion.

## ANGINA PECTORIS AND CORONARY OCCLUSION

The pain of angina pectoris and coronary occlusion is due to myocardial ischemia which results from a partial or complete occlusion of a coronary artery or one of its branches. The lumen of the vessel may be obstructed gradually by an arteriosclerotic plaque or suddenly by thrombosis or embolism. Syphilitic

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\* Assistant Professor of Medicine, Jefferson Medical College. Assistant Physician, Jefferson Hospital.



lesions in the wall of the aorta may encroach upon the orifice of a coronary artery. In either case there is a gradual or sudden obstruction of the blood supply to a portion of the myocardium.

A gradual obstruction may occur without pain, and may be manifested by no other symptoms than those commonly associated with myocardial weakness and failure. The victim first notices dyspnea resulting from physical tasks that were formerly accomplished without effort. Over a period of years he notices increasing breathlessness on slight exertion as the blood supply to the heart muscle is gradually and progressively impaired.

During the stage of partial occlusion, a sudden strenuous physical effort or mental excitement may result in a sudden severe pain of angina pectoris—the angina of effort. The amount of exercise necessary to provoke a pain usually decreases as the obstruction increases. The partially obstructed vessel which supplies sufficient blood during rest causes a partial ischemia when a greater volume is required during effort. It is not uncommon for such cases to be terminated by complete coronary occlusion. The pain of angina pectoris is variable in location and intensity. It may remain localized under any part of the anterior chest wall, but frequently it radiates down the inner surface of the left arm, less often the right arm. In fact, the pain may be entirely localized in the left shoulder, elbow, neck, or face. Numbness, tingling, and other sensory disturbances in the left arm, hand, or fingers may accompany the pain or be the only complaint. The intensity may vary from a slight indefinite sensation to an excruciating “viselike” pain.

#### Treatment

The pain of angina pectoris is of short duration, from a few seconds to a few minutes. Often it is readily relieved by discontinuance of all muscular effort. Amyl nitrite, 3 minims, by inhalation, or a tablet of glyceryl trinitrate (nitroglycerin),  $\frac{1}{100}$  grain (0.6 mg), placed under the tongue will give immediate relief. The latter is more convenient to administer and the effect is equally as prompt. The ampules of amyl nitrite are more costly, and its vapor permeates the air to the annoyance of all persons in the room.

Nerve sedatives have a beneficial influence in that nervous

tension is reduced and sleep is aided. Phenobarbital, given in  $\frac{1}{2}$ -grain (32 mg) doses three or four times a day, is convenient to use over a long period of time. Sodium bromide, 5 to 10 grains (0.3 to 0.6 gm), four times per day, often proves of value when the other sedatives fail.

Papaverine hydrochloride administered in  $1\frac{1}{2}$ -grain (0.1 gm) doses, four times daily, may reduce the frequency and severity of the attacks.

Good results have been reported following the intramuscular injection of testosterone propionate dissolved in sesame oil. Lesser used 25-mg doses every second to fifth day, depending on the frequency and severity of attacks, for a total of five to twenty-five injections. He reported no untoward reactions and all patients improved.

It is essential that the patient change his type of work to correspond with his ability to do it without pain. In fact he soon learns from experience the amount of physical effort that he can tolerate before pain appears. If the patient is overweight it is to his advantage to reduce the excess. Likewise, he should avoid large meals whether he is overweight or not. The added load on the circulation of digesting and assimilating a large meal often results in an attack of angina. In fact, deaths from such excesses are not uncommon, and in the past were usually reported as acute "dilatation of the stomach."

It is generally agreed that cigarette smoking is deleterious, alcohol, to the contrary, in moderate amounts is not injurious and in many cases affords relief from attacks of pain. Actually, the best outlook is for the patient who is willing to eliminate all excesses and reduce the strain of living to a minimum. This should include adjustment of his physical, financial, sexual and mental loads.

Surgical procedures such as total thyroidectomy and paravertebral injections of alcohol intended for the relief of intractable pain of angina pectoris require careful selection of cases and very often are attended with a great deal of risk. They should be attempted only by those especially trained in the technic.

#### CORONARY OCCLUSION

It is not uncommon for the attacks of angina pectoris to terminate in coronary occlusion, although in many instances the

attacks of pain may disappear entirely after the patient begins to show evidence of myocardial insufficiency. Likewise, the pain may recur after the myocardium regains its former tone.

The site and the character of the pain of coronary occlusion is just as variable as the pain of angina pectoris. It may be centered entirely in the epigastrium. In this location it has been confused with acute upper abdominal emergencies, occasionally leading to surgical exploration. The frequently associated symptoms of nausea, vomiting, leukocytosis and fever contribute to the picture.

The duration and intensity of pain vary in wide limits. In general, a pain lasting for more than fifteen minutes is suspicious of coronary occlusion. The intensity varies from a slight retrosternal oppression to an excruciating, prolonged constriction with a feeling of impending dissolution. The pain due to angina pectoris is almost always associated with an elevated blood pressure. If the blood pressure falls soon after the pain begins, coronary occlusion must be suspected. However, the fall in blood pressure may be delayed for several hours or even a day. The degree and rapidity of fall largely depend upon the severity of the attack. The pulse rate usually remains unchanged during the pain, the temperature may increase one or two degrees accompanied by a leukocytosis of 12,000 to 18,000. After a few hours the rate of sedimentation of the red cells becomes increased, although this may be delayed for several days. A pericardial friction rub may be heard if the infarct involves the anterior ventricular surface. The heart sounds may become fainter. Gallop rhythm and frequent premature beats may be present although the heart sounds often reveal no perceptible change.

The changes in the electrocardiographic pattern usually confirm the diagnosis, occasionally such changes are delayed or absent in the ordinary leads. Recently the American Heart Association recommended multiple chest leads in all cases suspected of having myocardial infarction.

#### The Management of Coronary Occlusion

The immediate treatment of myocardial infarction consists of the adoption of all methods to reduce the work of the myocardium to the absolute minimum. Rest should be enforced and it should be continued for four to six weeks. The use of the

bed pan and urinal should be insisted upon. However, in the case of very obese patients, the use of the bed pan may require more physical exertion than the use of a commode arranged near the bed.

Pain is best relieved by morphine in  $\frac{1}{4}$ -grain (16 mg) doses repeated as often as necessary. Pantopon,  $\frac{1}{3}$  grain (20 mg), or dilaudid,  $\frac{1}{12}$  grain (5 mg) may be used in the same way. Papaverine hydrochloride in  $1\frac{1}{2}$  grain (0.01 gm) doses has been found effective when administered intravenously. Papaverine is used for its antispasmodic action on the coronary arteries. Its analgesic effect is negligible in therapeutic doses. Atropine sulfate has been found of value to counteract the action of the vagus which induces reflex spasm of the other coronary vessels. The usual dose is  $\frac{1}{100}$  grain (0.6 mg), repeated several times a day. Atropine is contraindicated if the heart rate is rapid.

The inhalation of oxygen is a life-saving measure and often affords relief from pain, dyspnea and cyanosis. The concentration of oxygen in a tent should be maintained at 50 per cent or higher. This requires an oxygen flow of at least 9 liters and preferably 10 liters per minute. For relief of pain or circulatory failure, higher concentrations may be required. Such concentrations may be obtained by use of the B.L.B. or Barach-Eckman masks.

Cardiac arrhythmias complicating myocardial infarction add to the seriousness of the condition. Frequent ventricular premature beats may initiate fibrillation of the ventricle. Ventricular tachycardia, which is less common, may result in myocardial failure. Either condition can be controlled by the administration of quinidine sulfate, 3 grains (0.2 gm), every three hours. Quinidine is a myocardial depressant and it must be used with great caution.

Digitalis should be used only when signs of myocardial failure are evident. The increased force of ventricular contraction produced by digitalis may result in myocardial rupture. Also, its use in full doses may initiate arrhythmias which result in ventricular fibrillation.

#### ACUTE LEFT VENTRICULAR FAILURE

Dyspnea is the cardinal symptom of left ventricular failure. Usually it appears only after exertion, but it may appear while

the patient is at rest, or even awaken him from a deep sleep. It may be periodic, transient, or persistent. In fact, the initial warning may be a severe attack of paroxysmal nocturnal dyspnea with pulmonary edema. Various conditions such as vascular hypertension and chronic valvular defects, which add a great load to the work of the left ventricle, are predisposing factors which often lead to failure.

Primary acute right ventricular failure is comparatively uncommon and usually it is secondary to chronic pulmonary disease, embolism, or pneumonia. It is more often seen in conjunction with left ventricular failure due to conditions which cause degeneration of both sides of the heart. Arteriosclerosis, hypertension, syphilis and chronic rheumatic valvular disease are the most common predisposing factors.

Frequently mild attacks of nocturnal dyspnea are mistaken for bronchial asthma. Such attacks may be repeated for several months before their true origin is recognized. In other instances, however, the first indication of serious cardiac disease may be a severe paroxysm of nocturnal dyspnea with pulmonary edema. The patient suddenly awakens with a feeling of suffocation and coughs frothy, blood-stained sputum. The fluid accumulates rapidly in the lungs and bronchi causing loud gurgling rales. The skin becomes cold, moist and cyanotic. The pulse is rapid and the blood pressure falls. Recovery from such attacks is not uncommon, and they may or may not be repeated.

#### Treatment

No single measure is more successful in this emergency than the injection of  $\frac{1}{4}$  grain (15 mg) of morphine sulfate. Usually its administration is followed by the immediate relief of the anxiety, cough and dyspnea. Frequently no other treatment is necessary except rest for several weeks. If signs of myocardial insufficiency persist, the prompt use of digitalis is indicated. It may be given by mouth,  $4\frac{1}{2}$  grains (0.3 gm), at six-hour intervals for four or five doses. If more rapid action is desired, digitaline Nativelle by oral administration of a total of from 1.25 to 1.5 mg given in fractional doses, 0.25 to 0.5 mg at intervals of from four to six hours. Ouabain (G-strophanthin) may be administered intravenously if still more rapid action is desired. The dose for intravenous use is  $\frac{1}{250}$  grain (0.25 mg). Neither

of these preparations should be used if the patient has had digitalis previously

Venesection is useful to relieve the load on the right ventricle by decreasing its output. The same effect may be obtained by applying tourniquets to the four extremities. These should be released alternately every few minutes. This procedure traps the venous blood in the limbs, consequently prevents its return to the right side of the heart. Oxygen is a valuable aid in preventing the deleterious effects of anoxia on the tissues. It should be administered by means of a mask to obtain a concentration of 70 to 100 per cent. Such concentrations have been found to be highly beneficial in emergencies. However, many patients will object to the tightly fitting mask. The tent is more comfortable for the prolonged administration of oxygen, and valuable in an emergency if it is readily available. A concentration of 50 per cent can be maintained within a tent if the flow is regulated to at least 9 and preferably 10 liters per minute. To obtain maximum benefits from oxygen therapy, the oxygen concentration of the air in the tent should be tested at frequent intervals. The temperature and humidity in the tent should be regulated to the patient's comfort.

In the absence of other equipment in an emergency, oxygen may be administered by means of a nasal catheter passed into the nasopharynx. A concentration of nearly 40 per cent may be obtained by this method. The oxygen should be passed through at least 3 inches of water to moisten the gas and prevent drying of the mucous membranes. Ordinary industrial oxygen is the same as oxygen used in medical practice.

Aminophylline, 3 grains (0.2 gm), may be used to prevent attacks of nocturnal dyspnea. However, the intravenous mercurials, salyrgan and mercupurin, have been found to be more effective and reliable. Their greatest value is found in the prevention of those attacks of nocturnal dyspnea associated with chronic congestive heart failure. In such cases they should be used in conjunction with one of the acid-producing salts, such as ammonium chloride. This should be given in a total of 80 to 90 grains (5.3 to 6 gm) in divided doses each day for two or three days prior to the intramuscular or intravenous use of the mercurial.

Following recovery from an acute attack of nocturnal dysp-

nea, the routine treatment for myocardial insufficiency should be followed for two to four weeks

Attacks of acute ventricular failure are often precipitated by the added strain on the left ventricle as a result of surgical operations or acute illnesses. The modern custom of overloading the circulation by the administration of large volumes of saline and glucose solutions before, during, or after operation is often the final straw. Such fluids should be given slowly and in moderate amounts, as needed. The routine postoperative care should be abandoned, and individual care ordered when the patient presents any evidence of left ventricular weakness, or any of the conditions which predispose to it. Either during an acute illness or in the postoperative period, a constant watch should be kept for signs of left ventricular strain. Early signs consist of crepitant rales at the bases of the lungs, increasing pulse and respiratory rates. The early and judicious use of digitalis and oxygen will prevent a more serious, if not a fatal collapse.

#### PAROXYSMAL TACHYCARDIAS

These conditions are recognized by their abrupt onset and termination, and their great regularity. During a paroxysm the rate may vary from hour to hour but there is no variation between the beats. These ectopic rhythms may originate either in the auricle, the A-V node, or the wall of the ventricle. Their exact origin can be determined only by means of an electrocardiographic tracing. Paroxysmal tachycardia of ventricular origin is usually associated with organic heart disease, but it may be induced by toxic doses of digitalis. The commoner varieties—auricular and nodal tachycardias—usually occur in otherwise normal hearts. The duration of the attacks may be short and frequently repeated, or they may continue for several days.

#### Treatment

Many attacks are of such short duration that no treatment is required. In the more severe episodes, the patient is greatly distressed by the tumultuous heart action and several methods may be attempted before one is successful. All methods of treatment depend upon the same principle—stimulation of the vagus. Patients who have had repeated attacks often learn a

simple method which is effective in controlling the attacks in their particular cases. Such procedures include a forcible attempt to expire, after deep inspiration with the glottis closed, or an attempt at inspiration under the same conditions. Either method should be repeated several times until successful. Induced vomiting is often successful, this may be accomplished by use of an emetic drug such as syrup of ipecac, 2 fluidrachms (8 cc), or by irritation of the glottis with the finger or other object. Pressure on the eyeball may be effective. Stimulation of the carotid sinus by means of pressure with several fingers is more certain. The carotid sinus is located approximately at the level of the upper border of the thyroid cartilage. Pressure should be applied by means of two or more fingers over the right carotid artery, if unsuccessful the procedure should be repeated on the left side.

Several drugs having a vagomimetic effect have been used, and in certain cases any one of them may be effective when others fail. Acetyl-beta-methylcholine chloride (methylol) in the dose of 5 to 50 mg by subcutaneous injection often gives prompt relief. The small dose should be tried first. Large doses may cause profuse sweating, salivation and lacrimation. If these ill effects become alarming they are promptly controlled by the hypodermic administration of  $\frac{1}{100}$  grain (0.6 mg) of atropine sulfate.

The hypodermic injection of prostigmine methylsulfate, 1 cc of a 1:2000 solution, has been found to be effective in certain cases. Physostigmine salicylate has a similar action but it is not so effective.

If the attack persists, quinidine sulfate may be used. It should be given in 3-grain (0.2-gm) doses every two or three hours, after a single initial dose to test for sensitivity to the drug. Recently Sturnick and his associates (J.A.M.A., 1943) prepared a soluble preparation of quinidine suitable for parenteral administration for treating acute cardiac arrhythmias when vomiting, collapse, or unconsciousness precluded oral administration. They report excellent results in the treatment of paroxysmal tachycardia with this preparation.

In severe cases of tachycardia with impending myocardial failure, digitalis is indicated. It may be given by mouth in full doses, or if more rapid action is required one of the pure glucosides, strophanthin or ouabain, may be given parenterally.



## HEART BLOCK (STOKES-ADAMS SYNDROME)

Stokes-Adams syndrome is included as a cardiac emergency because of the possibility of its sudden onset without previous warning. It must be stressed that the characteristic attacks with syncope and convulsions are extremely rare. There are many minor degrees of the condition, however, which may be manifested by a slight faintness or vertigo which passes off in a few seconds, or may be more prolonged and the patient falls unconscious. The severity of the symptoms depend upon the duration of the cerebral ischemia. This results from cessation of ventricular activity when the transition occurs from normal auriculoventricular conductions to complete block. In the severe attacks the appearance of the patient may have a striking resemblance to an epileptic seizure. The skin may be cold, moist and cyanotic. The veins become greatly distended. After the paroxysm, recovery is usually rapid, and without residual effects. This helps to distinguish it from an apoplectic attack in which there is persistent paralysis.

The diagnosis of Stokes-Adams syndrome is confirmed by the very slow heart rate, usually under 40 per minute, the brevity of the attack, and prompt recovery. Occasionally additional confirmation may be had by comparing the pulsations counted in the distended jugular veins, which correspond to auricular contractions, with the ventricular rate counted at the wrist or the apex of the heart. The electrocardiographic pattern is characteristic and the final word in the diagnosis.

## Treatment

In most instances Stokes-Adams syndrome is so brief that no treatment is necessary. However, the frequency of attacks may be reduced by administering drugs which increase the excitability of the idioventricular pacemaker from which impulses arise in the absence of the normal auriculoventricular pathway. Epinephrine has been found to be effective in relieving the attacks. It should be administered hypodermically in 0.5- to 1-cc doses of the 1:1000 solution. Ephedrine sulfate may be used in the same manner, the dose is  $\frac{1}{8}$  to  $\frac{3}{8}$  grain (20 to 25 mg). It has the advantage of having a more prolonged effect, although it is not so powerful. Ephedrine sulfate is especially useful in preventing the recurrence of attacks. It should be

given by mouth in the same dose, three or four times daily. Its use may be continued for months or years if necessary.

Barium chloride,  $\frac{1}{2}$  to 1 grain (30 to 60 mg) three times daily by mouth, is an older remedy and its value has not been confirmed by experience.

Atropine sulfate,  $\frac{1}{100}$  grain hypodermically, may be used for the relief of an attack.

The underlying cause should receive proper treatment. In most cases this is coronary sclerosis or rheumatic endocarditis. The older idea that many cases were due to luetic heart disease with gummatous lesions encroaching on the bundle of His has not stood up in the light of modern investigation. Of course, if the blood Wassermann test is positive, the patient should receive proper antiluetic therapy.

## EXTRACARDIAC VASCULAR EMERGENCIES\*

DOUGLAS W LUND, M D

THE vascular emergencies arise from occlusion of vessels or rupture of vessels. In many diseases which are generally insidious or primarily extravascular, there may occasionally develop vascular abnormalities which are emergencies. It is not practicable, however, to deal with such exceptions in detail.

Hemorrhage is the escape of blood from the normal confines of the vascular system. It becomes an emergency when the total loss is great enough to interfere with the normal functions of an individual, or when the hemorrhage is into certain tissues, interfering with specific processes. This latter form of hemorrhage will be dealt with in relation to those organs where its occurrence, along with thrombosis, embolism and vasospasm, results in impairment of function indicative of the organ involved.

### HEMORRHAGE

Gross blood loss may occur externally, where it is easily detectable, or internally, into a large body cavity, where it is concealed. In either case, the hemorrhage may produce the syndrome of shock, or if the blood loss is not excessive or rapid, it may simply produce a secondary anemia. Although there is individual variation, the rapid loss of 750 cc (approximately  $1\frac{2}{3}$  pints) of blood may give evidence of approaching shock. A more gradual loss of blood will result in a fall in the erythrocyte count, and will usually produce no frank symptoms until far advanced.

*Symptoms and Signs*—Anemia secondary to hemorrhage is characterized by pallor, particularly of the mucus membranes. Generalized weakness and dizziness are frequent. The temperature may be subnormal at first and slightly elevated later. Complaints such as headache, syncope, nervousness or somnolence may result from the cerebral ischemia. The blood changes are, of course, diagnostic.

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\* From the Department of Medicine, Jefferson Medical College.

Despite the ability to observe external hemorrhage and to appreciate by the methods of physical diagnosis a collection of blood in a body cavity, excessive blood loss is frequently not suspected until signs and symptoms of approaching shock have occurred. The patient may complain of chilliness, insatiable thirst, or weakness. Pallor is an early and very constant sign due to constriction of the peripheral vessels. The veins are collapsed, and blanching following digital pressure disappears slowly. The skin, particularly of the extremities, is cold and moist. The nail beds and finger tips are pale. Restlessness may be severe, yet it may change rapidly to apathy and somnolence. The pulse rate is rapid and may become thready or imperceptible as shock advances. Diarrhea and enuresis are occasionally observed. Finally, the unfailing evidence of advancing shock is a progressive fall of blood pressure. The systolic pressure may be sustained for a considerable period above the critical level of 75 to 90 mm of mercury. With continued bleeding the pressure will fall rapidly, resulting in a shock-like state and death.

*Laboratory Diagnosis*—Within a period of one-half to two hours following blood loss of several hundred cubic centimeters, there is often an elevation of the total leukocyte count and an increase in the younger leukocyte elements. A drop in the erythrocyte count and hemoglobin content occurs more gradually. Furthermore, the approach of shock is accompanied by hemoconcentration. This is more evident in that syndrome of shock where the loss of blood is not a factor. A patient bleeding rapidly may die with little fall in the erythrocyte count or hemoglobin concentration. Following severe hemorrhage, hemodilution is appreciable in a few hours and reaches a maximum in about forty-eight hours. Since this change permits the amount of blood loss sustained to be estimated at a later date, it is best immediately to obtain a complete blood count at the advent of hemorrhage and repeat this at appropriate intervals of from one to several hours.

#### Treatment

The initial objective in hemorrhage is the stemming of the loss of blood. Where a shock-like state is imminent it is necessary to replace the volume of blood by the intravenous or the

intrasternal route *Whole citrated blood* compatible with that of the patient is the fluid of choice. However, owing to the factors of availability and facility it may be necessary and prudent to use *plasma*. In shock resulting from hemorrhage, the isotonic plasma is best, but when concentrated plasma is more readily available, this may be used. The equivalent of 500 cc of whole blood is from 15 gm to 17.5 gm of plasma protein, i.e., about 250 cc of the undiluted plasma. In the treatment of severe hemorrhage, it may be necessary to give 2000 to 2500 cc of whole blood, or 4 to 5 units (15 gm to 17.5 gm. per unit) of plasma.

The use of isotonic salt solution, with or without glucose, is not advised, since the elements needing replacement are the plasma protein and erythrocytes. When the above solutions are not available, the following substances have been recommended: (1) human serum, which, due to less protein content, is less efficacious than the plasma, (2) purified human albumin, or (3) solutions of pectin, which are generally not available at the present time, (4) solutions of acacia which are rarely, if ever, indicated.

The *general measures* for hemorrhage are adequate sedation of the restless patient, and conservation of body heat. The application of heat exceeding normal body temperature is to be deplored, since the damage sustained by the tissues may of itself aggravate the syndrome of shock. Peripheral constriction is a mechanism by which the vascular system adjusts itself to the decreased blood volume. It is ill advised to interfere with this process by applying excessive heat to the point of overcoming this constriction.

The drugs which cause vasoconstriction (i.e., epinephrine, ephedrine, pitressin, benzedrine, and strychnine) have been advocated and are briefly efficacious, however, their use may be followed by a fall in blood pressure supposedly due to fatigue of the vasoconstrictory mechanism. The use of suprarenal cortical extract has not yet proved of practical value. If blood is being replaced, the inhalation of oxygen, or better, oxygen (90 per cent) and carbon dioxide (10 per cent) gas, would seem logical, in view of the tissue anoxia accompanying hemorrhage and shock.

There would seem to be little advantage in the old practice

of binding the limbs tightly, since elevation of the foot of the bed, with the head and thorax dependent, will provide the maximum of circulating blood to the vital organs

*In summary*, the treatment of hemorrhage (volume of blood lost) is (1) to stop the bleeding, (2) to replace the blood loss, (3) to conserve the body temperature, and (4) to allay restlessness

#### VASCULAR OCCLUSION AND LOCAL HEMORRHAGE

In a consideration of vascular emergencies, other than volume loss of blood, attention is directed to regional changes in circulation and structure of the vascular system. The flow of blood to any part depends chiefly on the normality of the local vessels, nevertheless, it is also influenced by the competence of the general circulation, the sympathetic nervous system, and the element of individual reaction. Conditions which threaten the competence of the local vessels do so either by obstructing the normal flow of blood (thrombosis, embolism and vasospasm), or by creating a rupture of the vessel with resultant hemorrhage into the tissues. Frequently one or all of these mechanisms may operate at the same time, or in sequence. For example, an embolus may lodge, induce hemorrhage, stimulate vasospasm, and, in the resulting stasis of blood, initiate thrombus formation.

*Local hemorrhage* occurs from trauma, or from weakening of the vascular wall usually by arteriosclerosis, syphilis, or aneurysm. Certain blood dyscrasias such as leukemia, polycythemia vera, hemophilia, purpura, and in certain instances the metabolic and infectious diseases encourage the onset, and aggravate the course of hemorrhage.

*Thrombosis* in a vein is usually the result of circulatory stasis. This is associated with prolonged inactivity, local injury to the vessel by trauma or infection, or changes in the blood constituents favoring coagulation. Arterial thrombosis is most frequently initiated by the presence of arteriosclerosis, infection, or aneurysm.

*Embolism* occurs when a section of a thrombus in either a vein, artery, or the heart loosens and is carried away in the blood current, lodging elsewhere. It may be sterile or carry the organisms of infection. For example, in endocarditis the causative

organism may be carried to the point of embolization. Air or fat emboli entering the blood stream following widespread trauma or operative procedures are occasionally encountered.

*Vasospasm*, or prolonged vasoconstriction, may result from cooling, from the action of certain drugs or endocrine substances, from the irritation of sympathetic nerves, and from factors not clearly defined at present. The example of vasospasm in an arm resulting from the pressure of a cervical rib is well known. The occurrence of cerebral vasospasm is questioned by some authorities. Supposedly it occurs in association with embolism and thrombosis, or, in an isolated manifestation with hypertension. In the latter case the degree of hypertension may not parallel the degree and persistence of vasospasm.

#### PERIPHERAL ARTERIAL OCCLUSION

*Symptoms and Signs*—Occlusion of an artery in an extremity is usually characterized by the sudden onset of pain, and by the absence of pulsations distal, and often for some distance proximal to the point of occlusion, the latter due to vasospasm. There is pallor and coolness of the cutaneous surface. Weakness of the extremity approaching paralysis may occur. Numbness or paresthesias are frequent. The veins tend to remain collapsed. Blanching of the skin created by pressure or by elevating the extremity remains for a long period following release of pressure or lowering of the limb. In obstruction of the large vessels, the syndrome of shock may be pronounced, this is particularly true where embolism has occurred. Where occlusion has developed gradually, as in many instances of thrombosis, pain may be absent or mild, but the evidence of reduced arterial circulation will be present.

*Diagnosis*—Although simple arterial occlusion should not be confused with venous occlusion, in view of their differential aspects, difficulty arises when phlebitis induces an associated arterial spasm, obscuring the palpable arterial pulse. This is usually a temporary phenomenon. Where necessary, oscillographic determinations will reveal pulsation when they are so feeble as to escape palpation. Short of surgery such a patient should be treated for the more serious arterial occlusion until vasospasm is relieved.

### Treatment

The patient suffering acute occlusion of an artery should be immediately placed in bed. The extremity should be kept level with, or slightly below, that of the patient's heart. The entire body should be kept warm to encourage reflex vasodilation, but excessive heat should not be applied directly to the involved limb. If a covered cradle equipped with electric light bulb is placed over the limb, the circulating air within should not exceed  $38^{\circ}\text{C}$  ( $100.4^{\circ}\text{F}$ ). To apply excessive heat directly to tissue in which the blood supply is limited is to invite further injury.

In the recent literature there have appeared descriptions of a method for controlled refrigeration of an extremity involved in arterial occlusion. Although some promising results have been recorded, it would not seem advisable to recommend such procedure at the present time for use outside the facilities of a hospital.

Certain drugs may cause vasodilation and should be tried. Papaverine hydrochloride may be given intravenously in amounts from  $\frac{1}{4}$  grain (0.016 gm) to  $\frac{1}{2}$  grain (0.03 gm), or in double these amounts subcutaneously or orally. The medication may be repeated every three to six hours. The brief effect obtained upon inhaling ampules of amyl nitrite, or upon the sublingual administration of nitroglycerin,  $\frac{1}{100}$  grain (0.6 mg), makes their use of questionable value. They may well be tried at the outset of treatment, particularly in the instance of embolism. The oral administration of methyl- $\beta$ -acetylcholine in dosages of from  $\frac{1}{4}$  to 1 grain (0.016 to 0.06 gm) repeated when necessary, has been recommended. Should severe side reactions be encountered with this drug, these may be terminated by the administration of atropine. Ethyl alcohol in doses from  $\frac{1}{2}$  to 1 ounce (15 to 30 cc) mixed with fruit juices every four to six hours acts frequently as an excellent and prolonged vasodilator and sedative.

The employment of heparin in most cases should be carried out only in a hospital with full laboratory facilities. A thorough appreciation of the contraindications involved in the use of this drug is essential. A fatality from the induced prolongation of clotting time may result.

Since much can be done by embolectomy toward saving an



endangered extremity in embolism, recourse to consultation with a surgeon should not be delayed. Certainly, in the case of embolism, if no improvement is noted within four to six hours, surgical removal of the clot should be considered. It is stated that embolectomy is not successful after twelve hours.

For the purpose of securing vasodilation in a lower extremity an operation which may be considered is that of sympathectomy, or the injection of the appropriate sympathetic ganglia. A brachial plexus block may be used where an upper extremity is involved.

When gangrene has occurred, decision for operative procedures is primarily surgical. In elderly, arteriosclerotic, or diabetic patients, particularly in those who manifest severe toxicity, there is much to say for the recently proposed tourniquet and refrigeration anesthesia.

#### PERIPHERAL VENOUS THROMBOSIS

*Symptoms and Signs*—The clinical picture of venous occlusion varies not only with the size and position of the vessel involved, but with the presence or absence of inflammation. Pain is an outstanding symptom where inflammation, particularly periphlebitis, is severe. The absence of pain in venous thrombosis of the noninflammatory type may mask the involvement of even so large a vessel as the femoral vein. The first warning in these cases may be the occurrence of pulmonary embolism, or the complaint of edema of which the patient becomes aware after leaving bed for the first time.

In acute thrombophlebitis, symptoms are frequently rapid in onset. Where a large vessel is involved there is usually severe pain in the extremity, with acute tenderness over the course of the involved vein. The patient objects to passive movement of the limb. Edema and cyanosis are variable in degree, but when present are characteristic. Mild fever, leukocytosis, and an elevated pulse rate may or may not be present.

*Diagnosis*.—In instances of thrombosis in the small veins of the lower leg, dorsiflexion of the foot and kneading of the calf muscles frequently elicit tenderness when other evidence of involvement is lacking. Palpation along the large venous trunks will elicit pain. There should be little confusion between the symptoms and signs of venous thrombosis and those of arterial

occlusion When thrombophlebitis of a large vessel in its early stage is accompanied by arterial spasm, diagnosis may be difficult The procedure to be followed has been outlined under the discussion of Peripheral Arterial Occlusion

### Treatment

The objects of therapy in venous thrombosis are to prevent detachment of the clot, to relieve the patient of discomfort, and to reduce or prevent edema of the involved extremity In rare instances, where there is good reason to suppose that bacterial invasion has occurred, the trial of a sulfonamide drug is probably justified, but when the invading organism is not susceptible to this drug, its continued employment may be harmful

The patient should be kept at rest with the extremity sufficiently elevated to prevent edema An anodyne such as acetyl salicylate orally in doses of 5 to 10 grains (0.03 to 0.06 gm) may be given Occasionally the use of morphine may be necessary

The use of vasodilating drugs was discussed in connection with arterial occlusion and they may be used similarly to counteract spasm in venous thrombosis Both in arterial and venous occlusion, the application of excessive heat is to be avoided The use of warm, wet packs in the treatment of thrombophlebitis has been accepted by many physicians, but care should be exercised to avoid a temperature higher than 38° C (100.4° F) Warming the body, and not the involved limb, is the safest method of obtaining vasodilation.

In many cases the angiospasm and accompanying pain in thrombophlebitis may be relieved by the surgical procedure of injecting the appropriate sympathetic ganglia Where thrombosis of a large vein, usually the femoral, is evident, certain surgeons advocate that the vein be opened and the thrombus sucked out Another procedure is the ligation of the vein proximal to the thrombus Decision in such cases will rest with the surgeon The use of heparin for thrombophlebitis, though a routine procedure in some hospitals, can hardly be recommended for use where full laboratory facilities are unavailable

The patient with venous thrombosis should be kept in bed and under treatment until tenderness has disappeared and the pulse rate and temperature have remained normal for several

days Movement of the extremity should be reinstated gradually. If edema occurs when the leg is dependent, an elastic bandage should be worn while the patient is up, and removed when he is recumbent At night the involved extremity may be elevated

### PULMONARY EMBOLISM AND THROMBOSIS

The position of the lung in the vascular circuit renders it extremely vulnerable to embolism Any embolus originating within the major venous system, from the right chamber of the heart or pulmonary artery, has free access to the lung Fortunately, the structure of this organ is such that it may function adequately, despite widespread vascular occlusion Severity of reaction depends upon the size of the occluded vessel, and the competence of the collateral circulation derived from the bronchial arteries For example, pulmonary congestion due to heart failure renders the lung abnormally sensitive to vascular occlusion, and, to the degree of vascular stasis, favors thrombosis.

*Symptoms and Signs*—Typically, the initial evidence of an embolus is sudden pain, tightening or oppression in the thorax, often located beneath the sternum Anxiety is pronounced Pallor, frank cyanosis and dyspnea follow The skin becomes moist and cold The pulse is rapid, thready, or imperceptible. The blood pressure falls rapidly In severe embolism the clinical picture is chiefly that of shock Almost invariably, the complete obstruction of the main stem of the pulmonary artery results in death

If the patient survives the initial stage of shock, or if it is not severe, evidence of the pulmonary involvement may be more prominent The pain may be pleuritic in nature and source. It may be located along the lateral thoracic wall, aggravated by inspiration and accompanied by a friction rub Cough may be annoying Bloody or blood-streaked sputum is a characteristic but not constant finding Its appearance is frequently late

Occasionally an area of dullness may be demonstrated on percussion Moist rales are sometimes audible Often evidence of consolidation, both by physical diagnosis and roentgenographic study, is not present for hours or several days after vascular occlusion has occurred A murmur or thrill over the second costal interspace to the left of the sternum may occasionally be

detected There may be demonstrable dilation of the right ventricle

*Diagnosis*—The advantage of knowing of an antecedent condition within the patient which could result in embolism cannot be overemphasized The finding of such conditions (e.g., thrombophlebitis) after pulmonary embolism has occurred is of similar assistance Former mild pulmonary complaints accompanying lesser embolic episodes, which escaped diagnosis, will be recalled to great advantage at the advent of major pulmonary infarction Occlusions of small vessels in the lung are most frequently not diagnosed Pulmonary infarction may be misinterpreted as early lobar pneumonia or coronary occlusion The absence of a sufficiently elevated temperature, and the absence of pneumococci in the sputum will aid in the differentiation of the former Resort to repeated electrocardiographic studies to differentiate coronary occlusion may be necessary Certain changes in the electrocardiograph are indicative of pulmonary embolism

#### Treatment

The object of conservative therapy is to allay distress and restlessness The patient should be kept quiet in bed, with the head and shoulders elevated Sedation is essential Morphine sulfate in doses up to  $\frac{1}{4}$  grain (0.016 gm.), repeated as frequently as is necessary, is the drug of choice The use of papaverine hydrochloride in the manner discussed under treatment of vascular occlusion has been recommended Oxygen is indicated, and is administered best in the tent, but the use of a nasal catheter or mask may be necessary Since pulmonary congestion and the danger of shock coexist, the letting of blood is contraindicated Where an operating team is available to perform immediate embolectomy, this procedure may be considered in certain instances.

For pain of pleuritic type, particularly when it is located over the lower thorax, a scultetus or simple binder may bring relief, without the added discomfort of adhesive straps

The use of heparin to prolong coagulation time is advocated by some authorities Such treatment is prolonged over several days and carries an element of risk An initial intravenous dose of heparin may be given, prolonging coagulation time until the

patient can be transported to a hospital where heparinization is to be continued. The indications for use of heparin are sufficiently controversial to preclude a discussion here. The delayed effects of the drug, dicoumarin, do not recommend it for emergency use.

### MESENTERIC VASCULAR OCCLUSION

The occlusion of a vein or artery in the mesentery results in infarction with necrosis of the intestinal wall. The condition is an emergency of utmost importance since early diagnosis and surgical intervention may mean recovery from an otherwise almost universally fatal condition. Thrombosis in a vessel is usually the result of inflammation transmitted from a neighboring structure.

*Symptoms and Signs*—The patient complains of acute abdominal pain. Early, this may be located in the upper abdomen. Frequently it is generalized. Nausea and vomiting occur. As infarction advances, the abdomen becomes distended. Early forceful peristalsis may subside and paralytic ileus becomes evident. The abdominal pain characteristically becomes less severe and constant, and mild spasmodic pain takes its place. Diarrhea and bloody stools are the characteristic but late manifestations. A rapid pulse, leukocytosis, fever, and malaise occur as the condition progresses. Peritonitis is the usual complication. Shock may be profound in massive involvement.

*Diagnosis*—The sequence of abrupt onset, generalized abdominal pain, and bloody stools is characteristic. When an antecedent predisposing factor to embolism (e.g., rheumatic heart disease) or to thrombosis (e.g., recent abdominal surgery) is not apparent, it may be impossible to differentiate mesenteric infarction from other so-called acute intra-abdominal conditions. Surgical exploration may be necessary to reveal the diagnosis.

*Treatment*—Treatment is surgical. The adjunctive use of heparin should be considered.

### MISCELLANEOUS VASCULAR OCCLUSIONS AND INFARCTIONS

Occlusion of the *central artery of the retina* is infrequent. In the characteristic case there is sudden and complete blindness in the involved eye. Pain is absent or minimal. On ophthalmoscopic examination the characteristic picture of a cherry-red spot at the fovea with peripheral blanching is observed.

Delay in treatment may well result in permanent blindness. The physician should resort to the immediate use of vasodilating drugs. An ampule of amyl nitrite by inhalation affords rapid but brief effect. Nitroglycerin in the dose of  $\frac{1}{100}$  grain (0.6 mg) may be given sublingually, but should be followed by the longer-acting vasodilators, which have been previously discussed. Gentle massage of the eyeball has been recommended. One of the earliest recommended uses of heparin was in this condition.

*The spleen* is frequently the site of infarction, but in many instances the occurrence is asymptomatic, or masked by vascular occlusion elsewhere, such as in the lungs. The chief symptom is local pain, which is occasionally severe. Where perisplenitis occurs, tenderness on inspiration or a friction rub may be detected over the organ. The spleen may be slightly enlarged. Very infrequently the lodgment of an infected embolus will result in splenic abscess, in which case continued fever and chills are indicative.

*The kidney* is frequently subject to infarction. Gross or microscopic hematuria may be the only indication of such happening, or there may be no hematuria. In severe involvement, pain and tenderness may be present in the costovertebral angle, flank, and lateral abdomen. Treatment is symptomatic and directed to the source of embolism.

*The adrenal gland* particularly in the newborn, or during meningococcal meningitis, is subject to internal hemorrhage. The signs and symptoms closely parallel those of Addisonian crisis, and treatment of both conditions is similar.

#### CEREBROVASCULAR ACCIDENTS

Vascular occlusion and hemorrhage within the brain are intimately associated with the complex anatomy and function of this organ. Even a brief discussion of all areas which may be involved, is not practical in the space allotted. There is, however, a similarity in the clinical pictures of most so-called cerebrovascular accidents, and the treatment directed toward the cerebral involvement in most instances will not vary. Usually the etiologic factor arises in a generalized diseased process (e.g., hypertension) or in the diseased process of a remote organ (e.g., endocarditis). Effective action is determined chiefly by consideration of these causes.

Certain disease conditions which have much in common will be considered together. Of the many cerebrovascular diseases which are clinically dissimilar, only those which are common, and those which may require treatment as an emergency will be discussed. The accompanying tabulation is offered in an at-

### TABULATION

#### DIFFERENTIAL DIAGNOSIS IN CEREBROVASCULAR ACCIDENTS

	Hemorrhage	Thrombosis	Embolism	Subarachnoid Hemorrhage
Age	40-50	50 (and over)	10-40	20-40
Onset	Sudden	Gradual	Sudden	Often gradual
Blood pressure	Elevated	Normal	Normal	Normal or elevated
Spinal fluid	Clear or blood tinged	Clear	Clear	Bloody
Eye grounds	Papilledema Hypertensive changes Arteriosclerotic changes	Arteriosclerotic changes	Normal, or embolic phenomena	Normal Hypertensive changes Papilledema

*Note* The differential points indicated above are only generally applicable, and wide variation is often encountered.

tempt to bring out certain differential points, which are only generally applicable.

#### CEREBRAL HEMORRHAGE, THROMBOSIS AND EMBOLISM

*Symptoms and Signs*—Frequently the initial evidence of critical cerebrovascular accident is sudden loss of consciousness. This may have been preceded for minutes or days by variable headache, dizziness, generalized weakness, a sense of pressure in the head, anxiety, or speech disturbances. In many cases, by the time the patient is found or the physician is called, coma or stupor exists.

Characteristically, the face is flushed, the limbs relaxed, the pulse bounding, and the respirations stertorous. The patient may exhibit convulsions of the whole body, or only of one or more limbs. Incontinence of urine and feces is frequent. When stupor exists, the patient may respond in a drunken manner.

Examination frequently reveals absence of the corneal, abdominal and plantar reflexes. The eyes may fix to one side. The pupils are sometimes dilated or unequal, but may be normal, or

constricted. The chief clue to diagnosis rests in demonstrating a hemiplegia involving the face, tongue, or extremities. The fact that unilateral weakness and paralysis is seldom realized early by the patient, emphasizes the necessity for a detailed physical examination. Paralysis in the early comatose stages is usually of the flaccid type. With recovery of consciousness, there is a gradual change to spastic paralysis. Correspondingly the tendon reflexes, which are usually diminished or absent during coma, become hyperactive as the patient recovers.

*Diagnosis*—In typical cases of cerebrovascular accident the history of antecedent disease, such as hypertension, or a valvular heart lesion, coupled with the mode of onset and the finding of unilateral central nervous involvement make the diagnosis fairly easy. In obscure instances, differentiation will usually depend on defining the cause of coma.

The so-called "uremic coma" may be clinically indistinguishable from cerebrovascular accident without resort to determination of nitrogenous retention in the blood. Hypertensive encephalopathy is usually accompanied by high blood pressure, characteristic arteriolar changes in the retina, and cupping of the disk. It may or may not be associated with nitrogenous retention. The urinous odor of the breath and changes in the eyegrounds are helpful.

The coma of diabetic acidosis may be differentiated by finding low values for the carbon dioxide combining power of the blood, large amounts of sugar and acetone in the urine, and high values for the level of the blood sugar. However, it should be emphasized that an elevated blood sugar (rarely above 200 mg per 100 cc) with glycosuria, frequently occurs in cerebrovascular accident. In diabetic coma the cherry-red color of the lips and fruity (acetone) odor of the breath may be helpful.

Epilepsy, in view of the brief and intermittent episodes, should occasion little confusion. Hysteria presents features of its own, and is not accompanied by impaired corneal, abdominal and plantar reflexes. Drug poisoning and alcoholism may be difficult to exclude. Here again, the antecedent history, and absence of unilateral central nervous involvement will be helpful. Obviously, an alcoholic odor to the breath does not exclude the presence of a cerebrovascular accident.

Lumbar puncture for diagnosis is frequently justified. Usually



no more than a few cubic centimeters of fluid should be removed. Reference to the table on page 1554 may be of aid in interpreting the findings.

### Treatment

The patient with mild or severe manifestations of cerebrovascular accident should be placed in bed in quiet surroundings. The head should be elevated and turned to one side to facilitate breathing. Sedatives, other than the opiates, may be necessary to allay restlessness. The use of sodium bromide, and paraldehyde by mouth or rectum, or the use of sodium phenobarbital subcutaneously is satisfactory. Whether the patient eats, drinks, or moves his bowels is of little importance during the first twenty-four or forty-eight hours. Certainly food or drink should not be given beyond the patient's ability to accept it easily. Traditionally, a saline cathartic is recommended, but excessive purgation is ill advised. Where fluid is not taken for twenty-four hours, 1000 to 2000 cc of normal salt solution may be administered by vein or by hypodermoclysis. Where paralysis of the pharyngeal muscles persists beyond the first two or three days, feedings through a small stomach tube may be started.

The intravenous administration of solutions of *d*-glucose in the amounts of 50 cc of the 50 per cent, or 250 cc of the 20 per cent solution in an effort to relieve intracerebral pressure is of questionable value. In severe cases relief frequently follows, however, certain authorities believe that the final effect may be detrimental or at least inconsequential. Large amounts of glucose, unless saline is supplied parenterally, will dehydrate the patient whose intake by mouth is inadequate. The repetition of glucose administration should depend on the status and reaction of the patient. Drainage of the spinal fluid, gradually dropping an elevated pressure one half the distance to the arbitrary figure of normal (120 mm of water), will frequently relieve the increased intracerebral pressure. Here again there is disagreement as to the indications and final effect of such treatment. It would seem conservative to rely on the condition and response of the individual patient. In cerebral thrombosis, aspiration of spinal fluid is not indicated, and a fall in spinal fluid pressure may augment thrombosis.

Surgical intervention is not indicated except in the rare in-

stances of well localized hemorrhage. Decision usually depends on evidence of epidural or subdural bleeding.

#### EPIDURAL AND SUBDURAL HEMORRHAGE

*Signs and Symptoms*—The classical picture occurs when patient is knocked unconscious, recovers and remains symptom free (lucid interval) for a period of from several hours to several days and then gradually develops coma and progressive hemiplegia. Whether there is a "lucid interval" or not, the gradual progression of coma and nervous involvement is characteristic. Typically, the pupil on the involved side is enlarged. Paralysis of the body is, of course, contralateral. Clear spinal fluid is the rule in epidural hemorrhage, but bloody spinal fluid accompanies subdural hemorrhage.

*Treatment*—While the patient is under observation and before surgical intervention is instituted, the principles of treatment in the preceding section on cerebrovascular accidents should be adhered to. Sedation is often best avoided due to danger of obscuring important diagnostic evidence. When epidural or subdural hemorrhage is suspected, consultation with a neurosurgeon is indicated.

#### SUBARACHNOID HEMORRHAGE

In some instances subarachnoid bleeding has been described as spontaneous. Frequently, however, the causes of hemorrhage previously discussed are demonstrable. Congenital vascular defect and aneurysm may account for the frequency of this lesion in the younger age group. Undoubtedly, many cases are mild and escape recognition.

*Signs and Symptoms*—The patient may experience warnings such as dizziness, headache, or stiffness of the neck. Often, as in other cerebrovascular accidents, the onset is sudden, with loss of consciousness. Characteristically, the signs of meningeal irritation are present, for example, nuchal rigidity and positive Kernig's sign. These signs may not be manifest until the patient reacts from coma. Severe headache is common. Elevated temperature, rarely exceeding  $102^{\circ}\text{F}$  ( $38.9^{\circ}\text{C}$ ) is frequent, except in the initial stage of massive hemorrhage when subnormal temperature is the rule. Diagnosis is facilitated by the finding of a large amount of blood in the spinal fluid. This finding will

usually serve to differentiate subarachnoid hemorrhage from the other intracerebral accidents. A smear and culture of the spinal fluid will exclude meningitis when the presence of fever suggests this disease.

*Treatment*—The general measures are identical with those discussed under treatment of cerebrovascular accident. Spinal puncture is often of great aid in relieving severe headache and agitation. It should be performed as the need arises in the patient's status, and not on any routine schedule. The precautions for spinal puncture have been discussed under treatment in cerebrovascular accidents. Bed rest should be prolonged until the spinal fluid is clear and colorless. Prognosis as to recurrence should be guarded.

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## RENAL EMERGENCIES

BOLAND HUGHES M.D.\*

UNDER the term "renal emergencies" I shall consider not only some of the disease processes which affect the renal parenchyma itself, such as nephritis and pyelonephritis, but also acute urinary retention, anuria, urinary infections, urinary sulfonamide concretions, renal colic and hematuria. Any obstruction to the transportation of urine from the kidney to the bladder or from the bladder through the urethra may result in renal death just as certainly as primary renal parenchymal insufficiency. Hematuria should be considered a renal emergency because of the grave clinical implications attached to this symptom.

### PYELONEPHRITIS

Pyelonephritis is the most common disease of the kidney. All bacterial infections of the renal parenchyma and pelvis, excluding tuberculosis, are included under the general heading of "pyelonephritis."

#### Pathology

Weiss and Parker<sup>1</sup> have classified pyelonephritis into four groups according to its various stages: (1) acute pyelonephritis ("pyelitis"), (2) active chronic pyelonephritis, (3) healed diffuse pyelonephritis and (4) healed pyelonephritis with recurrence. It is questionable, however, whether pyelonephritis ever "heals," because even when the infection is quiescent, fibrotic contracture may be progressively destroying kidney function.

Acute pyelonephritis is not often observed pathologically, since nearly all patients recover. The pathological picture of active chronic pyelonephritis is that of chronic interstitial inflammation with atrophy of the tubules. The process may extend to the glomeruli causing fibrosis of the capsule and glo-

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\* Associate in Urology, School of Medicine, University of Pennsylvania, Chief of Clinic, Urological Service, Hospital of the University of Pennsylvania.

merular tuft and thickening of the basement membrane Arterio-  
lar fibrosis also occurs The entire kidney may become a mass  
of scar tissue This process may, of course, be unilateral or  
bilateral.

"Healed" diffuse pyelonephritis means that the patient is in  
a noninfectious stage In "healed" pyelonephritis with recur-  
rence, an active infection recurs and is superimposed upon a  
previous stage of the disease

The usual picture of "active chronic pyelonephritis" is that  
of partial obstruction of the urinary tract and an infection with  
organisms of low virulence If the infecting organisms become  
highly virulent, the pathological picture, of course, changes and  
cortical abscesses may occur If the urinary tract obstruction  
becomes too great, with the infecting bacteria remaining low in  
virulence, pyonephrosis frequently results

### Clinical Significance of Chronic Pyelonephritis

In a recent clinicopathological study<sup>2</sup> of sixty-two cases of  
uremia, on which necropsies were performed, chronic pyelo-  
nephritis was found to be responsible for the uremia in twenty-  
two cases In only three of these cases, however, had the diag-  
nosis been correctly made Lisa, Solomon and Gordon point out  
in this study that of all the types of renal disease which may  
result in uremia, pyelonephritis offers the best prognosis if diag-  
nosed early and if the proper therapy be instituted Every at-  
tempt must be made to eradicate the kidney infection in the  
*early stages of the disease*

Pyelonephritis has also a direct relationship to hypertension.  
Weiss and Parker<sup>1</sup> have estimated that in about one-half of all  
patients who die of hypertension, pyelonephritic changes are  
found in the kidneys and that *pyelonephritis alone is responsible  
for about 20 per cent of all cases of malignant hypertension*

### Clinical Picture of Chronic Pyelonephritis

*Initial Symptoms*—In a series of 172 cases of chronic pye-  
lonephritis reported by Nesbit and Conger,<sup>3</sup> 61 per cent had  
cystitis as the initial symptom and, of these, almost one-half had  
accompanying flank pain, either unilateral or bilateral Costo-  
vertebral pain alone was present in 17 per cent at the onset,  
sepsis alone in 4.6 per cent In this series, the symptoms existed

from three months to twenty years before pyelonephritis was diagnosed

*Infecting Organisms*—The colon bacillus is the most frequent invader in chronic pyelonephritis but any or many of a great variety of bacteria may be found

*Roentgenographic Changes*—The characteristic x-ray changes in the renal pelvis are due to the contractions of the inflammatory scar tissue and, therefore, occur only late in the disease and are definite evidence of irreversible kidney damage. The ureter may be irregularly dilated due to chronic inflammatory change

In the early stages of chronic pyelonephritis no morphological changes can be visualized by either intravenous urography or retrograde pyelography

*Renal Function*—In the very early stages of chronic pyelonephritis, none of the renal functional tests are sensitive enough to detect any impairment. As the disease progresses, renal function is definitely impaired, however. *The various functional studies provide the most accurate prognostic index*

### Treatment

All infections of the urinary tract are secondary to infections elsewhere in the body. The first axiom of treatment is, therefore, *to eradicate all foci of infection*. The second axiom is *to correct all urinary stasis which may be present*. Complete urological examination is, of course, necessary to determine whether urinary stasis is a factor. The third axiom is *to culture the urine or do a Gram stain on the sediment, to determine the type of infecting organism*. This guides one to more intelligent urinary chemotherapy. At the present time the best drugs for the treatment of urinary infection are mandelic acid and the sulfonamides

**MANDELIC ACID**—This is an excellent drug for colon bacillus infections and for *Streptococcus faecalis* infection. It is given in the form of ammonium or calcium mandelate. For the adult the dose is 12 gm of mandelic acid daily, for children, 1.25 gm per 10 pounds of body weight. The drug is best given in four divided doses

*A urinary pH of 5 to 5.4 is essential for bactericidal activity*. Though mandelic acid is excreted unchanged by the kidneys,

additional acidification by ammonium chloride is usually necessary to reach these pH levels. The usual plan is to give ammonium chloride for a day or two (2 to 3 gm daily) before administering the mandelic acid. After the mandelic acid therapy has been started, the ammonium chloride can usually be reduced to about 0.5 gm daily. *The pH of the urine should be checked daily.*

With mandelic acid therapy it is necessary to limit the fluid intake to between 1000 to 1200 cc daily in order that the necessary concentration of the drug (0.5 to 1 per cent) be reached in the urine.

If the urine cannot be sterilized in eight to ten days with this regimen, it is advisable to discontinue the drug. Sulfonamide therapy may be started or mandelic acid again administered after one week's rest.

**SULFONAMIDES**—Sulfathiazole and sulfadiazine are the drugs of choice.

**Sulfathiazole**—Sulfathiazole has bactericidal action on practically all types of organisms invading the urinary tract. It is superior, however, in its effect on the staphylococcus and Streptococcus faecalis.

**Sulfadiazine**—Sulfadiazine has superior bactericidal effect against the streptococcus, pneumococcus, Friedlander's bacillus and the colon bacillus group.

**Dosage**—An initial daily dosage of 3 to 4 gm of either sulfonamide is usually sufficient. After two to three days the amount may be reduced to 2 gm daily for a period of six to eight days. *In treating urinary infections we do not need the large amounts of sulfonamides which are necessary in systemic infections.*

If the urine is not sterilized in about ten days' time, use the other sulfonamide after a short rest period (three to four days) (or eventually try mandelic acid).

#### ACUTE URINARY RETENTION

Acute urinary retention may be due to (1) prostatic enlargement caused by carcinoma, adenoma, or abscess, (2) urethral stricture, (3) foreign body in the urethra, (4) neurogenic bladder dysfunction, particularly after acute cerebrospinal injury. To diagnose the cause of the retention one should palpate along

the course of the urethra to determine whether a foreign body is present. If a periurethral induration or abscess accompanies a urethral stricture, palpation of the urethra is a necessary diagnostic procedure. Rectal examination will determine the size and consistency of the prostate. A history of spinal injury or neurological disease should make one suspect the possibility of a neurogenic bladder. Neurological examination revealing any sensory or motor changes in the lower trunk or in the lower extremities should certify the diagnosis. The treatment of neurogenic bladder will be discussed later but in all other forms of urinary retention a 16 F soft rubber catheter should be gently inserted into the urethra and, if possible, into the bladder. If the catheter will not pass by an obstruction in the anterior or membranous urethra, one is very likely dealing with a urethral stricture, particularly if no foreign body has been palpated along the course of the urethra.

#### *Treatment of Acute Retention Due to Urethral Stricture*

To relieve the acute retention due to urethral stricture it is first necessary to pass a filiform through the strictured area into the bladder. *Woven Phillip's filiforms which can be threaded to a woven Phillip's urethral catheter* are preferred and are far safer than the old-fashioned whale-bone filiforms with the tunneled metal Gouley's catheter, which was threaded over the filiform. Woven Phillip's urethral catheters, threaded for the woven Phillip's filiform, should be available in sizes 8 to 28 F. After the filiform has been inserted through the strictured area into the bladder, an 8 or 10 F Phillip's catheter is threaded to the filiform and passed into the bladder to relieve the acute retention. The urethral stricture, of course, must then be subsequently dilated, preferably by again passing a Phillip's woven filiform and threading to it metal Le Fort urethral sounds (sizes 8 to 20 F). After the stricture reaches 20 F caliber, ordinary urethral sounds may then be used to dilate the stricture to the normal caliber of 32 F.

#### *Treatment of Acute Retention Due to Prostatic Enlargement*

##### *Types of Catheters*

- 1 Soft Rubber Catheters. These are the most commonly-used urethral catheters. Sizes 8 to 28 F should be available, the



8 or 10 F caliber being sufficiently small to use in a new-born male child. The Robinson catheter has two advantages over the ordinary soft rubber catheter. It has two eyes and its hollow tip permits the use of a metal stylet, the tip of which would slip out of the ordinary whistle-tip type catheter, in those rare cases of prostatic obstruction in which a semirigid rubber or a woven catheter cannot be inserted. Another advantage is that the catheter is made of latex rubber which is not as irritating to the urethra as ordinary rubber when used as an indwelling catheter.

- 2 Semirigid Rubber Catheters. These catheters are extremely practical for use in prostatic obstruction when the ordinary soft rubber catheter cannot be inserted. Sizes 12 to 24 F are advisable. The coudé, olive, solid tip assists the catheter in riding over the prostatic obstruction.
- 3 Woven Catheters. These are more rigid than the rubber type and are of the greatest value in cases of prostatic obstruction. Both the ordinary coudé-tip type, in sizes 6 to 30 F, and the modified natural curve, olive-tipped type, in sizes 10 to 24 F should be available.
- 4 Metal Catheters. These are used very infrequently by present-day urologists. Woven catheters have replaced the metal ones in relieving the retention of prostatic obstruction. (Owing to the great danger of urethral damage, a metal catheter should be used only by those experienced in urethral catheterization.)

*Decompression of the Bladder*—In any long-standing urinary retention, such as the chronic retention of prostatic obstruction or the acute retention developing from chronic prostatic retention, the bladder should be emptied gradually to prevent the fall of blood pressure and renal damage which sometimes occur if the retained urine is completely withdrawn from the bladder at the time of catheterization. In order to permit gradual adjustment of the blood pressure and bladder pressure to lower levels and to prevent renal damage from compensatory edema caused by the sudden lowering of intravesical pressure, the bladder should be gradually decompressed as follows.

The soft rubber catheter is inserted into the bladder with the end clamped to prevent the premature escape of urine. The catheter is then connected to a rubber tube about 6 feet long, which has been filled with sterile water and clamped at both

ends before being joined to the urethral catheter. This rubber tube is then connected to one of the arms of a glass Y-tube, which is inverted and fastened with adhesive either to the bed or another supporting object at such height above the distended bladder that, when all clamps are removed, a few drops of urine trickle through the inverted Y-tube when the patient takes a deep breath or voluntarily contracts his bladder. Another rubber tube is attached to the other arm of the inverted Y-tube and carries the urine to a drainage bottle. The Y-tube is gradually lowered every three to four hours as the blood pressure and bladder pressure readjust themselves.

Decompression usually takes about forty-eight hours. Bladder decompression is not necessary in postoperative urinary retention unless this is superimposed on a chronic prostatic retention.

If the bladder cannot be emptied by any of the above urethral measures, a *suprapubic cystostomy* becomes imperative. If, however, operative facilities are not available, suprapubic bladder puncture is indicated. To accomplish this a lumbar puncture needle should be inserted through the skin just above the symphysis in the midline. The needle is passed between the recti muscles and through the bladder wall. It should then be inserted about an inch and a half further into the bladder cavity so that complete emptying of the bladder will be facilitated. Bladder puncture, however, is only a temporary emergency procedure and should be followed by suprapubic cystostomy as soon as possible.

#### Management of the Neurogenic Bladder

Under this heading we are concerned primarily with the management of acute retention, following cerebral spinal injury. In the war of 1914 to 1918, 80 per cent of the American and English soldiers who sustained a paralytic bladder due to spinal cord injury died as a result of the bladder paralysis rather than of the spinal injury itself. *The cause of death was renal sepsis*, and this sepsis resulted from infection that was introduced into the bladder by urethral catheterization. It is therefore of paramount importance to reduce the incidence of urinary infection to an absolute minimum. A transverse lesion at any level of the cord or cauda equina usually results in three urinary phases: (1) retention, (2) incontinence of overflow, (3) automatic mic-

turition Urinary retention lasts for varying lengths of time, but gradually results in the incontinence of overflow This overflow incontinence should be prevented

To prevent renal infection and to relieve the acute retention before the incontinence of overflow occurs, the following rules should be observed

- 1 *Do not catheterize the bladder under any consideration*
- 2 *The urine should be manually expressed from the bladder every four hours* The bladder should be massaged from above downward toward the symphysis with the patient lying on his side The patient should strain to exert as much intra-abdominal pressure as possible at the time the bladder is being manually expressed *This schedule should be followed every four hours with religious punctuality* Manual expression is contraindicated only if the urine becomes infected Daily urine examinations should therefore be made
- 3 *Suprapubic cystostomy is indicated if manual expression be impractical or if urinary infection occurs* Suprapubic cystostomy reduces the hazards of ascending pyelonephritis to an absolute minimum and, of course, completely relieves the urinary retention

### Acute Retention Due to Foreign Body in Urethra

Treatment depends on the nature of the foreign body and its location in the urethra If the foreign body is small and is located in the anterior urethra, one may be able to remove it by grasping the foreign body with a long forceps or clamp inserted into the urethra If the foreign body cannot be easily removed in this manner, special urological treatment is necessary

### HEMATURIA

Hematuria is the outstanding symptom of urinary disease but too often its importance is underestimated by both the patient and his physician Frequently, hematuria is both painless and intermittent and it is the cessation of the bleeding which is the more dangerous factor, for this lulls the patient into a false sense of security and makes him think that he is well *As hematuria is merely a sign of existing disease, its occurrence demands immediate and thorough urological examination to determine the nature of the pathological process* When the bleeding is at the beginning of urination, the source is usually the anterior urethra,

occasionally the posterior urethra. *Terminal* hematuria usually originates in the posterior urethra or in the bladder. *Total* hematuria more often indicates that the bladder, ureter, or kidney is the seat of disease. One cannot, however, rely too much on the type and appearance of the blood.

Blood in the urine is an extremely serious symptom. MacKenzie in 1932 found that 75 per cent of the cases of hematuria were caused either by tumor, infection, calculus, or nephritis. In 96 per cent of the cases, the causative lesion was in the urinary tract and over 40 per cent of these lesions were neoplastic. In a small number of cases the cause of the hematuria is not found on the first complete urological examination (cystoscopy, estimation of the individual kidney function, examination of specimens of urine from each kidney, pyelography and intravenous urography). In eighty-nine such cases, however, as Cahill<sup>4</sup> has reported, re-examination at a later date found the causative lesion in fifty-five of the cases. Thus only a very small percentage could be classified as "essential" hematurias.

The following tabulation and grouping (Cahill) can be used to classify and to guide the study of hematurias.

- I Hematuria in general diseases
  - A Acute fevers especially in the severe forms, malaria, acute articular fever, scarlet fever, tonsillitis, etc
  - B Chronic infections
    - 1 Endocarditis (renal infarction)
    - 2 Purpura
    - 3 Syphilis
  - C Diseases of unknown etiology
    - 1 Hodgkin's disease
    - 2 Leukemias
    - 3 Periarteritis nodosa
  - D Vitamin deficiencies
    - 1 Scurvy
    - 2 Liver deficiencies
  - E Inborn anomalies
    - 1 Hemophilia
- II Hematuria from causes within the urinary tract
  - A Renal causes
    - 1 Congenital anomalies (polycystic disease)
    - 2 Injuries

- 3 Motility
- 4 Calculi or crystals
- 5 Infections
  - (a) Acute pyelitis, pyelonephritis
  - (b) Chronic pyelonephritis, nephrosis
  - (c) Specific tuberculosis
- 6 Nephritis
- 7 Parasitic diseases as filariasis
- 8 Tumors capsular, parenchymal, pelvic
- 9 Drugs turpentine, phenol, cantharides, methenamine, salicylates, sulfonal, barbiturates, organic acids as mandelic, sulfanilamide and other derivatives
- 10 Local vascular changes
- 11 Unknown origin
- B Ureteral causes
  - 1 Trauma
  - 2 Calculi
  - 3 Infection, ureteritis cystica, stricture
  - 4 Tumors
- C Vesical causes
  - 1 Malformation
  - 2 Trauma
  - 3 Calculus or foreign body
  - 4 Infections, including prostatic or urachal
  - 5 Parasitic as bilharziasis
  - 6 Tumors
  - 7 Epithelial changes as leukoplakia
- D Urethral causes
  - 1 Malformations
  - 2 Injuries
  - 3 Calculus or foreign body
  - 4 Infections
    - (a) Acute urethritis, chancre, chancroid
    - (b) Chronic urethritis, stricture
  - 5 Tumor
  - 6 Nevus
- III Hematuria from diseases invading the urinary tract
  - 1 Acute appendicitis
  - 2 Acute or chronic salpingitis
  - 3 Acute or chronic diverticulitis of the colon
  - 4 Intestinal or female genital tuberculosis
  - 5 Abdominal or pelvic tumors
  - 6 Extrarenal or extra-ureteral tumors

- 7 Perforations of gastric or duodenal ulcers
- 8 Perforations of aneurysms
- 9 Perforations from osteomyelitis

### RENAL COLIC

Any sudden blockage in the transportation of urine from the renal pelvis to the bladder may cause renal or ureteral colic. The most frequent cause of renal colic is sudden blockage at the pelvo-ureteral junction by a renal stone or sudden ureteral blockage by a small stone which has passed from the renal pelvis to lodge in the ureter. Renal colic may also occur when the ureter becomes acutely kinked due to a ptosed kidney. In a typical attack of renal colic, severe, intermittent, lancinating pain radiates from the lumbar region along the course of the ureter to the genitalia.

#### Diagnosis

A typical attack of renal colic can be readily diagnosed from the history and physical examination but this diagnosis *must be substantiated* by finding a *urinary obstruction* either by x-ray (to detect opaque stones) or by ureteral catheter (nonopaque stones) or by relieving the colic, when due to ptosed kidney, by placing the patient in the knee-chest position. Further confirmation of the diagnosis is the *presence of hematuria* (also from a ptosed kidney). Thorough urological survey will, of course, reveal the complete diagnosis and this should be done as soon as possible.

#### Treatment of Renal Colic

- 1 *Do not rely on morphine to relieve pain*
- 2 Administer papaverine hydrochloride hypodermically (0.03 gm) *to relieve spasm which is causing the pain*. Repeat dosage every half hour for three or more doses if necessary.
- 3 Place patient in a very hot bath. This sometimes completely relieves the colic.
- 4 Place patient in knee-chest position if "Dietl's crisis" from a ptosed kidney is suspected.
- 5 Insert a ureteral catheter to the renal pelvis *to relieve the obstruction*. Allow catheter to indwell.

- 6 If none of the above measures are effective, give the patient spinal anesthesia or intravenous anesthesia (sodium pentothal) for a short time
- 7 After complete urological examination determines the nature and location of the obstructive uropathy, surgical or instrumental means must be employed to correct the cause of the renal colic

#### URINARY SULFONAMIDE CONCRETIONS

Formation of and deposition of sulfonamide crystals in the renal tubules, renal pelvis and ureter may produce very serious urinary obstruction and result fatally. This is more likely to occur when the sulfonamides are used in large doses to treat severe systemic infections than in the treatment of urinary infections and is particularly prone to occur when the fluid intake, and thus the *urinary output*, is low. With a low urinary output the concentration of sulfonamide in the urine is greatly increased and precipitation of the crystals (particularly the acetyl form) is favored. Complete anuria may result when both ureters, or the tubules of both kidneys, are blocked.

#### Prevention

1 *Never let the urinary output fall below 1500 cc daily* when large doses are being used to treat systemic infections. If the output of urine falls below this level, stop the drug temporarily until the urine volume is increased.

2 *Administer alkalis* during the sulfonamide therapy to raise the urinary pH and thus increase the solubility of the drug in the urine. Sulfonamide solubility in urine is minimal from pH 5.6 to 6.6, is doubled or tripled at pH 7.5 and increased tenfold at pH 8.0. *Give sufficient sodium bicarbonate by mouth to keep the urinary pH at least at 7.5.* A constant check on the urinary pH (nitrazine paper) is necessary.

#### Treatment

1 *The occurrence of hematuria or lumbar pain* during sulfonamide therapy indicates the probability of sulfonamide concretions being present somewhere in the urinary tract. Sulfonamide concretions are nonopaque to x-ray.

2. *Stop the drug immediately*

3 *Increase the fluid intake and alkali administration*

4 *Catheterize one or both ureters to establish drainage from the renal pelvis* Catheters are allowed to indwell and the renal pelvis or pelvises are irrigated with sterile physiological saline solution

This procedure will not, of course, relieve the urinary obstruction from *tubular blockage*

5 If catheters cannot be passed into the renal pelvises, nephrostomy may be necessary if anuria is complete

### ACUTE NEPHRITIS

Acute nephritis may develop suddenly, presenting all the classic textbook features of the disease, such as hypertension, edema, pyrexia and hematuria, or it may be insidious in its onset, entirely escaping diagnosis unless the evidence of renal involvement is found on urine examinations

In making the diagnosis of acute nephritis, it must be remembered that, whereas hypertension, edema, nitrogen retention, uremia and convulsions are the main syndromes found in the acute stage, *abnormalities of the urine may be the only constant feature present* On the other hand, in the more severe forms of the acute disease, one must look for and be prepared to treat such complications as hypertensive encephalopathy and cardiac decompensation McIntosh<sup>6</sup> stresses the fact that a mild circulatory failure occurs more frequently than is realized in patients with nephritis and that care must be taken to spare the heart. The prognosis is proportional to the degree of circulatory failure

#### Treatment

Treatment of the acute form of nephritis must be largely symptomatic and is not standardized In general, psychic and somatic rest is necessary, hypertension should be controlled by magnesium sulfate, morphine may be needed, oxygen promotes the patient's comfort and aids in supporting the circulation, and digitalis may be of value if used with care. In more detail, the treatment should consist of (1) complete bed rest until hematuria, edema and albuminuria have disappeared, (2) dietary measures—restriction of protein and exclusion of fats in the early stages, and (3) restriction of fluids to 1500 to 2000 cc. daily



for a few weeks. One must remember that we are dealing with impaired renal function and attempts to "flush out" the kidney are futile. For convulsions, Roper<sup>6</sup> recommends venesections of 10 to 15 ounces of blood supplemented by rectal infusions of 4 ounces of 50 per cent magnesium sulfate. Bromides, chloral hydrate, and sometimes morphine may be necessary. Sometimes lumbar puncture may help. Winkler, Smith and Hoff<sup>7</sup> recommend slow intravenous infusion of 500 cc of 2 per cent magnesium sulfate solution for the treatment of convulsions. The injection may be repeated, but allowances should be made for decreased elimination of the drug by the diseased kidneys. Not more than  $3\frac{1}{2}$  ounces (100 cc) of 2 per cent magnesium sulfate solution should be given if renal insufficiency is severe, as respiratory failure may ensue.

Williams, Longcope and Janeway<sup>8</sup> recommend the use of sulfanilamide in the treatment of acute glomerulonephritis and have reported very good results with it. I feel it should be used in all acute cases and that it is the sulfonamide of choice. Only 1 to 1.5 gm should be given daily for one week.

I agree with the almost unanimously held concept that chronic glomerulonephritis is the result of the presence of more or less minimal unhealed lesions in the kidney following the acute process of the disease, and feel that the prognosis of acute nephritis is not as good as some would have us believe. The severity of the acute phase is no criterion in determining the prognosis. Murphy and Peters<sup>9</sup> have very ably outlined the management of the patient after the acute stage is over, as follows: (1) At least four months of bed rest, (2) a diet consisting of 0.75 to 1 gm of protein per kilogram of body weight, (3) restriction of sodium chloride intake to 5 to 6 gm per day, (4) adequate but not excessive fluid intake, (5) vitamins, especially A, B complex, C and D, plus iron medication, and (6) removal of foci of infection about one month after the acute episode.

#### ANURIA

The occurrence of anuria is of very serious clinical import, and demands immediate study to determine its cause. Proper treatment can be instituted only after the cause of the anuria is known.

In a general way we may classify anuria into three different groups

1 Secretory

- (a) Prerenal, such as when the causes are proximal to the kidney (circulatory failure, diminished fluid intake, shock, hemorrhage, etc.)
- (b) Renal, due to inadequate secreting renal tissue (acute nephritis, advanced hydronephrosis, polycystic kidneys, advanced pyelonephritis, acute nephrosis, etc.)

2 Obstructive or Postrenal

(a) Intrinsic

- 1 Ureteral blockage (bilateral)
- 2 Ureteral blockage in single kidney
- 3 Lower urinary tract obstruction as by tumors of the bladder and prostate

(b) Extrinsic

- 1 Ligation of the ureters during gynecological operation
- 2 Retroperitoneal tumors and neoplasms, particularly extension of carcinoma of the cervix

3 Composite Group

- (a) Traumatic injury of kidneys and ureters
- (b) Crush injury to limbs resulting in muscle necrosis and subsequent renal failure
- (c) Extensive burns

The immediate problem in the treatment of anuria is to determine as quickly as possible the type and cause of anuria. The obstructive type of anuria lends itself more readily to treatment and it is the treatment of this type that we shall briefly consider.

### Treatment of Obstructive Anuria

The diagnosis of obstructive anuria can be readily made from the history and physical examination. All our efforts should be directed toward locating and relieving the obstruction as soon as possible. The following are the steps which should be taken to accomplish this:

- 1 *Catheterize the bladder* to determine if any urine is in the bladder. (This also differentiates between acute retention and anuria.)
- 2 *Determine the presence of opaque ureteral or renal calculi* by a survey x-ray film of the urinary tract.

- 3 *Cystoscope the patient and catheterize both ureters to determine the patency of the urinary tract Leave catheters indwell after obstruction is overcome*
4. Unilateral or bilateral ureterostomy or nephrostomy is indicated if ureteral catheters do not relieve the obstruction

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## GASTRO INTESTINAL EMERGENCIES

GUY M. NELSON, M D \*

and

JOHN H HODGES M D †

THE purpose of this article is to discuss briefly and to re-emphasize some of the ordinary problems encountered in the diagnosis and treatment of the common gastro-intestinal emergencies. Improvement in diagnostic precision follows the knowledge of the usual findings, the atypical findings, and a thoughtful consideration of the differential diagnostic possibilities. The latter will not be included here. Improvements in treatment follow early diagnosis, the prevention and restoration of disturbances in fluid, food and electrolytic changes of the body, the proper use of drugs, and operative intervention when necessary.

### ACUTE PERFORATION OF PEPTIC ULCERS

Whatever the cause or causes of peptic ulcer, the incidence has risen, likewise perforation. It is amazing to note that there has been no significant improvement in the mortality rate in these cases in the past twenty years, despite the general progress in medical management of many other conditions. When one considers this, the fault appears to lie in the continued failure to make early diagnoses and to institute prompt surgical measures. In such a dramatic condition, this is a serious criticism of either our promptness or diagnostic acumen.

#### Diagnosis

In approximately 80 per cent of all cases, one is able to obtain a previous history of periodic pain and discomfort after eating, which was relieved by food or alkalies. It is true that in the

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\* Assistant Professor of Medicine, Jefferson Medical College. Assistant in Medicine, Jefferson Hospital.

† Fellow in Medicine, Jefferson Medical College.

other 20 per cent such a history may be entirely absent or too indefinite to be dependably suggestive

*Pain*—This dramatic episode appears suddenly, is severe and epigastric in location. It is referred in most cases either to the right, left, or both shoulder tops. It is highly important to learn of this early occurrence, because later the character of the pain and the general appearance of the patient change. At the onset the patient is still, usually is perspiring, is breathing with his chest, and is holding and protecting his abdomen, this is in contrast to the behavior of a person with colic. As time goes on, the pain becomes less severe and more diffuse, extending to those areas where the peritoneum is involved as the peritonitis spreads. In those cases where the perforation is anterior and distal to the midgastric region, the pain will extend down the right half of the abdomen, frequently confusing the picture with that of acute appendicitis. This is the result of the material extruded flowing down the right colonic region into the pelvis. Pain extends down the left side in those cases where the perforation is anterior and proximal to the midgastric region.

When the perforated area is in the upper right abdominal quadrant, the great omentum may localize the process, but the history of this distinctive, early, sudden, severe pain precedes the less severe localized pain which follows.

Frequently the posterior perforations become localized but the history of sudden, severe pain precedes the less severe pain which follows when localization is complete. The latter is quite apt to be colicky and referred to the back. Rivers has said "When the pain of gastric ulcer shifts definitely to the left, slightly upward or to the back, when the pain of a duodenal ulcer shifts to the right, upward, over the area of the liver or through to the back, one can correctly assume deep penetration or partial perforation of the lesion."

In the diagnosis of acute perforation the most important aid is a careful history, which includes a sudden severe pain, often following the ingestion of food, changing in its character and in its distribution according to the position of the perforation. One cannot stress too much the meticulous care with which the history should be obtained and the importance of obtaining this before the picture is confused by hours of illness.

*Temperature and Pulse*—Early, both are apt to be depressed, later they are affected by the complicating peritonitis, diagnostically these are not important.

*Tenderness and Rigidity*—These findings are of equal importance with the history of pain. Boardlike rigidity has been described and is usually found. On the other hand, it may be much less than boardlike and early, may be confined chiefly to the upper abdomen or may disappear entirely just after the patient has reacted from shock. When the lesion is localized in the upper right quadrant, the findings are those of tenderness and rigidity, much as one would find in acute cholecystitis. In those cases where perforation is localized posteriorly the tenderness and rigidity are localized to the upper part of the abdomen and are less marked. In most of the anterior perforations these findings are present in the epigastrium in typical form and spread down the abdomen either to the right or left side and gradually become general, when general peritonitis has had time to develop. It is in these cases that rectal palpation is of such great value. As the peritonitis spreads, rectal tenderness is found bilaterally.

*Liver Dullness*—In those perforations where a sufficient amount of air is extruded, the area of liver dullness is decreased. This may be verified by x-ray studies. Its absence should not influence one's diagnosis, its presence is helpful.

*Peristalsis*—The abdomen is usually silent.

*Leukocyte Count*—Early, the polymorphonuclear cells may be normal or increased, later, as peritonitis develops, they are increased almost without exception.

### Treatment

The most important acts in successful therapy are a diagnosis made before the sixth hour, the immediate entrance of the patient into a hospital and prompt surgical intervention. After the sixth hour, the mortality rate rises rapidly and there are many who feel that surgical intervention is unnecessary if delayed fifteen hours.

Morphine sulfate should be given hypodermically in sufficient amounts to relieve the patient and make him reasonably comfortable. Usually it requires  $\frac{1}{2}$  grain (0.032 gm) or more.

In order that the gastric contents may be prevented from being expelled into the peritoneal cavity, immediate intubation should be performed and continuous gastric suction maintained.

It is well to place the patient on the left side in the hope that one may be able to control partially the spread of the peritonitis to the left, instead of to the hepatic region.

Plasma (if unavailable, a 5 per cent solution of acacia) is used intravenously to combat shock, and 5 per cent glucose in normal salt solution to maintain fluid balance. It is rarely necessary to administer more than 16 to 32 gm of the former and 1000 cc of the latter prior to operation, unless the patient is seen late in the course of the illness.

In cases where the process has extended beyond the stage of chemical peritonitis the intravenous or possibly the local use of sulfonamides is indicated.

A general survey of all the organs of the body should be made and supportive therapy used, when needed. This especially applies to the heart, lungs and kidneys.

#### GASTRO-INTESTINAL HEMORRHAGE

Acute gastro-intestinal hemorrhage of emergency degree may arise from many causes, the chief one of which is peptic ulcer. Other causes are esophageal varices, malignancy, diseases altering the hemostatic properties of the blood, inflammation such as acute gastritis, foreign bodies, and severe acute febrile diseases including malaria, yellow fever, and "malignant" scarlet fever.

#### Diagnosis

Symptoms are dependent upon the rapidity and amount of bleeding. In the adult the immediate loss of 60 cc of blood is sufficient to cause melena, and the rapid loss of more than 300 cc is likely to cause subjective symptoms. Hematemesis and melena are nearly always present, singly or combined, where hemorrhage is of emergency degree. Usually blood persists in the stools for days after bleeding has stopped. Usually vomiting of blood may be accepted as evidence of active bleeding. Faintness is often an early perception and may be followed by dizziness, perspiration, weakness, pallor, thirst and loss of consciousness. As bleeding continues, the patient becomes apprehensive and restless, the blood pressure falls, the pulse rate increases,

and progression to an imminent or actual shocklike state follows

### Treatment

*Absolute Bed Rest*—This condition is terrifying and is accompanied, as a rule, by great environmental confusion. Statistical data vary considerably about its seriousness. It is our feeling that most patients, if their cases are properly supervised, survive. Often there is the harmful tendency to be too attentive, disturbing the patient's rest and causing increased anxiety, and to administer fluids and blood prior to their need. Obviously the patient should be placed in a hospital, the head lowered and the body surrounded with warm coverings.

Quiet lessens the circulatory requirements and the tendency to bleed. These patients are constantly in danger and require careful and capable nursing. In the first twenty-four hours the blood pressure and pulse should be estimated every one-half hour to one hour, thereafter according to clinical indications, sudden massive blood loss may precipitate a crisis which, if unnoticed, may be irreversible. Progressive rises in pulse, especially if it reaches 130 per minute, or a fall in blood pressure below 90 to 80 mm of mercury systolic or 50 to 40 mm diastolic, with clinical evidence of a failing circulation, warrants a consideration of the use of fluids.

*Parenteral Fluids*—Potentially, *whole blood* is the most important. Typing and cross-matching should be performed when a bleeding patient is first seen, regardless of the possibility of cessation of hemorrhage. No one can foretell the circulatory status of the immediate future. Three hundred to 500 cc of citrated blood may be given intravenously in one-half to one hour in the event of a rapidly falling blood pressure or increasing pulse rate. In our opinion this should not be done until there is clinical evidence of a maintained circulatory stabilization (three to five days as a rule) unless blood is required to maintain vital functions incompatible with living. With a stabilized blood pressure it may be administered with greatest value at a rate of 100 to 150 cc. an hour.

*Plasma* may be administered intravenously, by syringe, for incipient or actual shock. The dose is 16 gm diluted in 45 cc of sterile distilled water, injected over a period of not less than



five minutes Repeated administrations of this amount of plasma may be given every fifteen minutes to an hour as indicated clinically.

*Saline solution* (with or without glucose) should be started immediately, temporarily, when blood or plasma is suddenly necessitated but not yet available Parenteral saline and glucose solution may be used to replace or supplement the oral fluid intake It is unnecessary to give the saline-glucose solution (except in emergency states) until the twenty-four-hour urinary output has dropped below the 500-cc level or in case of acidosis It is advisable to administer it slowly in 500-cc amounts every six to twelve hours, the total twenty-four-hour amount and the time-intervals for its administration depending upon the urinary findings

*Intramarrow injection* may be indicated where venous puncture is impossible and it is desirable to place fluid in the vascular system Up to six years of age the tibia is the ideal site for marrow injection, after six years the sternum is preferable.

Red blood cell counts and hemoglobin determinations should be done once or twice a day to aid clinical judgment as to when transfusion is indicated in the absence of shock Early in the course of this condition they are not as quickly reliable as the general clinical picture, the blood pressure and pulse, because it requires several hours for the blood to readjust itself to the hemoconcentration following blood loss When the arbitrary levels of 2,000,000 to 2,500,000 red blood cells or 35 to 50 per cent hemoglobin (5.6 to 8 gm) are reached and the circulation stabilized, slow transfusion of 500 cc of whole citrated blood (100 to 150 cc per hour) may be indicated every two or three days until the red cell blood count has reached the 4,000,000 level

*Sedatives*—Sedatives should always be given to the point of insuring mental and physical quietude in these cases where apprehension and restlessness so commonly occur. They must be repeated often Barbiturates, such as sodium phenobarbital in 1½- to 2-grain (0.1 to 0.13 gm) doses, if well tolerated, may be more effective than morphine sulfate (⅓ to ¼ grain [8 to 16 mg]) Experimentally, morphine tends to cause excess relaxation of the duodenal wall and probably has the same effect on other nonsphincter portions of the gastro-intestinal tract How-

ever, in actual practice, morphine remains the choice of the majority of clinicians

*Fluids and Food*—Most accepted methods of administration may be classified under two headings (1) starvation, (2) immediate feeding

### 1 STARVATION

This means a complete deprivation of food and drink usually for three to five days until hematemesis and clinical evidence of bleeding have disappeared. During this time, parenteral fluids are relied upon to maintain fluid balance and to furnish a small amount of nourishment. Sedatives are required at frequent intervals for comfort. Despite the recent trend toward immediate feeding, starvation is frequently the first choice, especially in those cases seen early following hemorrhage.

Statistical reviews would incline one toward the immediate feeding of patients with hemorrhage. When successful, this method causes the patient to lose less weight and decreases the total number of days of incapacity. On the other hand, such data can be misleading and personal experience should influence one in making a choice of methods. One of us has seen several deaths in patients who were fed promptly, as against one death in that group which were not. As a consequence we prefer initial starvation followed by one of the first two methods listed below

#### (a) Modified Sippy Diet (Alkalies)

Equal parts of milk and cream to make 3 ounces (90 cc) are given hourly from 7 00 A.M. to 9 00 P.M. Sodium citrate (3 to 5 gm per liter) may be added to milk in case cream is not tolerated

Calcium carbonate (2 to 4 gm [30 to 60 grains]) is given hourly with milk and cream or between the feedings in 2 to 3 ounces (60 to 90 cc) of water

The feedings combined with 4 gm (60 grains) of calcium carbonate are given every two hours during the night.

Magnesium oxide, 1 gm (15 grains), is given two to five times daily in place of the carbonate to prevent fecal impaction.

With this regimen one must watch for alkalosis. With the onset of signs, immediately stop all alkalies and increase fluid and chloride intake

## (b) Andresen Gelatin-Milk Mixture

	Amount	Carbo- hydrate	Fat	Protein	Calories
Gelatin	30 gm			27	100
Glucose	60 gm	60			240
Cream (20%)	100 gm	3	18	3	180
Milk	900 gm	36	27	27	550
		<u>99</u>	<u>45</u>	<u>57</u>	<u>1070</u> approximately

## Feedings after hemorrhage

- 1 No feeding during sleep
- 2 No water, ice, or other drinks
- 3 At time of serving, such flavors as chocolate, vanilla, coffee, or tea may be added

## 4 Serve cool or warm as follows

1st and 2nd days	4 oz q 1½ hours
3rd, 4th and 5th days	5 oz q 2 hours
6th and 7th days	5 oz q 2 hours

Now add to each of four feedings one of the following

1 soft-boiled or poached egg, 3 oz cereal, custard, jello, ice cream

8th and 9th days As above, but add two extras to each of three feedings

10th day and on  
Water

Ulcer diet  
Start on 5th day—  
1 oz at a time  
and increase  
daily ½ oz  
½ oz each night  
starting on 2nd  
night

Mineral oil

## 2 IMMEDIATE FEEDING METHODS

(a) Meulengracht Method Institute promptly on admission to hospital

## (1) Puree diet

6 00 A.M. Tea, white bread and butter

9 00 A.M. Oatmeal with milk, white bread and butter

1 00 P.M. Dinner—meat balls, chops, vegetables, applesauce, tapioca pudding, omelet, etc

3 00 P.M. Cocoa

6 00 P.M. White bread and butter, sliced meats, cheese, etc., tea

## (2) Sodium Bicarbonate,

Mag Subcarbonate

Ext Hyocymus

1 teaspoonful t.i.d

ââ 15 gm  
2 gm

## (3) Lactatus ferrosi, 0.5 gm t.i.d

(b) Aluminum Hydroxide by Intubation (after Woldman)

- (1) On admission pass soft nasogastric tube to lower end of esophagus and begin drip of  $33\frac{1}{3}$  per cent suspension of colloidal aluminum hydroxide at 15 drops a minute, day and night, for ten days. If the patient is unable to tolerate the tube, give 1 ounce (30 cc) every hour during the night.
- (2) Soft bland diet every two hours.
- (3) Mineral oil daily or enema every other day for constipation.

*Vitamins*—Vitamin K is indicated in 1- to 2-mg doses daily intramuscularly, if a deficiency exists (blood prothrombin below 50 per cent). Vitamin C is given in 300-mg doses daily, orally or intravenously, if scurvy is present (or orange juice—16 ounces).

*Surgical Intervention*—Exploration supported by the use of parenteral therapy during and after operation is indicated in cases of peptic ulcer with hemorrhage at any time (without delay) when transfusions fail to maintain a sufficient number of red blood cells and hemoglobin to carry on the vital functions of the body. Ligation of the bleeding vessel is necessary. The small group of bleeding ulcer cases failing to respond to medical therapy tends to be in the ages beyond forty-five years. Splenectomy is often curative and life saving in splenic anemia and thrombocytopenic purpura.

#### ACUTE CHOLECYSTITIS

In this discussion we are concerned only with those cases which may or can become surgical emergencies. The statistical data on this type of disease are probably very different from those which might be collected by the general practitioner. Acute cholecystitis is a more common condition than it is generally thought to be. Fully 98 per cent of the cases are associated with gallstones. The pathological picture appears to be one of obstruction, inflammation, and a mechanical disturbance of the blood supply, due either to pressure on the vessels produced by the stone, or to the resulting infiltration and edema of the gall-bladder itself, or both. Most physicians would prefer elective management of this condition, regardless of whether they favor surgical or medical procedures. We suggest that all acute proc-

esses be observed closely until the danger of gangrene, empyema and perforation has been determined. We do not subscribe to the belief that the pathological processes cannot be evaluated by the clinical picture. It is our feeling that usually the mistaken diagnoses result from a failure to make a careful and detailed study of the process as it develops. Undoubtedly in many instances this failure occurs because the physician is called late, but it should serve as a warning to us that we may not be negligent in our observations of the process as it evolves.

### Diagnosis

*Pain*—Acute cholecystitis is ushered in by an attack of colicky pain, beginning in the epigastrium and radiating to the right hypochondrium and to the tip of the right shoulder blade. In perhaps 5 per cent of cases the pain may radiate to the right shoulder tip. Gradually the pain becomes more localized over the gallbladder region, is less severe but constant. Early, the patient is apt to be restless and to thrash about, but later he guards himself and prevents the upper abdomen from moving, even to the point that respiration is thoracic. In a very small percentage of cases the pain begins mildly, is more of a discomfort and may be indefinite in its localization.

*Anorexia*—It is almost a constant occurrence.

*Nausea and Vomiting*—In over half of the cases nausea or vomiting, or both, are present at one time or another.

*General Appearance*—Usually anxiety is expressed and if the process is extending, a toxic, apathetic appearance is highly suggestive of arising complications.

*Distention*—Very early this may be absent, but notoriously these patients swallow air and, later, as the toxic process develops peristalsis is affected, causing distention, the result of mechanical and bacterial changes. It is our feeling that this, more than anything else, accounts for the confusing and conflicting findings when palpation is attempted.

*Tenderness and Rigidity*—Over the involved area tenderness and rigidity can be expected to follow if inflammatory changes are present. The extent should depend upon the acuteness of the process, the involvement of the outer coat of the gallbladder, the presence or absence of protecting organs such as the omentum and the position (superficial to deep) of the gallbladder.

itself Logically, colic without tenderness can be assumed to be free of inflammatory changes Likewise, increasing tenderness and rigidity will follow increasing inflammatory processes As complications develop, exquisite tenderness with definite muscle guarding is present.

*A Palpable Mass*—This is a most important diagnostic sign. As the inflammation progresses the gallbladder enlarges and localized peritonitis follows, the great omentum may try to protect and localize the process By careful palpation this is revealed as a more or less definite finding The importance which can be attached to this definite or indefinite mass ("inflammatory cake") may depend upon the findings of previous examinations as one watches the course of the disease

*Fever and Chills*—In the ordinary case of acute cholecystitis there is no chill. The temperature rarely rises above 100° F In the presence of complications, fever and chills usually occur, indicating serious developments such as empyema or gangrene

*Leukocytosis*—A polymorphonuclear leukocyte increase is almost always present and usually ranges between 15,000 and 25,000

*Jaundice*—In approximately 20 per cent of cases this is present, but it does not necessarily mean that there is a stone in the common bile duct More often there is not It may result from torsion and bending, inflammatory changes, or a stone in the common bile duct, or possibly a hepatitis

#### Treatment

All cases should be observed at least once in twenty-four hours until it is certain that the process has subsided If, after forty-eight hours, one is uncertain the patient should be carefully examined every twelve hours All therapy is based upon the principle that elective surgery (or in case of debility, the prevention of surgery) is preferable. Each case, therefore, should be individualized instead of choosing the more risky attitude of immediate surgery in all cases

*Bed Rest*—This should be complete, except for bathroom privileges in selected cases

*Food*—A low fat, high carbohydrate, high protein diet should be used In case of nausea and vomiting, complete gastric rest is advisable, substituting for it the intravenous administration

of a 10 per cent solution of glucose in distilled water or normal salt solution (2000 to 3000 cc in twenty-four hours). As soon as it is possible skimmed milk, fruit juices, gelatine preparations, and junket are substituted in small quantities every two hours, making the total daily intake sufficient to cause an excretion of 1000 cc of urine in the twenty-four-hour interval. In this way, dehydration and acidosis will be prevented.

*Elimination*—Bland enemas are usually the most satisfactory. If gastric tolerance permits, any nonsaline laxative such as the fluid extract of cascara 1 to 2 drams (4 to 8 gm), compound licorice powder 1 to 2 drams (4 to 8 gm) and the like may be used.

*Local Applications*—Large, thick flaxseed poultices, applied over the entire abdomen, usually give more comfort than any other application. They may be applied for a one-hour period every six to twelve hours, depending upon how much the skin can tolerate.

*Medication*—For colic give morphine sulfate hypodermically or beneath the tongue in  $\frac{1}{4}$ -grain (0.016-gm) doses, as often as needed. For discomfort and less severe pain a capsule containing  $\frac{1}{2}$  grain (0.032 gm) of codeine sulfate,  $\frac{1}{12}$  grain (0.005 gm) of extract of belladonna and 5 grains (0.325 gm) of acetylsalicylic acid given every three to six hours may be all that is necessary. Sedatives, such as phenobarbital or one of the bromides, may be useful in producing relaxation and in obtaining rest.

*Care of Other Organs*—In case the prothrombin time is less than 50 per cent, it is important to administer vitamin K in 1 or 2 mg doses by mouth, or into the muscles, or directly into the veins every two hours for two or three times until the test is normal. Occasionally it is necessary to administer whole blood when the damage to the liver cells makes the vitamin K inert.

When the total blood protein is lower than 6 gm per 100 cc one may use human blood plasma, whole blood (or perhaps one of the newer amino-acid preparations which are beginning to offer promise) to improve or correct this state.

In those cases where the urobilinogen content of the urine is present in a dilution greater than 1 to 20, or where there is evident impairment in the ability of liver cells to excrete dye (bromsulf-

alein) or its bile pigment, 10 per cent glucose in normal salt solution or distilled water should be administered intravenously daily in 1000- to 3000-cc amounts. The greater the damage to the liver cells, the more glucose is required. It is important to maintain the blood sugar at a high level in such cases in order that the glucose may be converted into glycogen and stored as a protective agent in the diseased liver cells.

*Sulfonamides*—At the present time it appears that their use is contraindicated, inasmuch as nausea, vomiting and other toxic effects which may follow their use may be confused with the possibility of an extension of the process, and since from a mechanical standpoint the drugs would fail to reach the involved strangulated part.

*Surgical Intervention*—Almost always this condition requires surgical methods, unless the risk involved, when one considers the patient as a whole, is greater than the risk of the condition being considered.

Emergency intervention is necessary in those cases in which the sum total of the general appearance of the patient, the temperature, white blood count and the localized findings, especially that of a palpable mass, make one feel that the process is extending and approaching a state where a dangerous complication may occur.

Fortunately, elective surgery can be performed in many cases of cholecystitis, at a time when the acute process has subsided and all abnormal factors have been corrected, insofar as it is possible. This allows the surgeon the freedom to work in a less infected field and to choose those technical procedures which will insure the best possible result.

#### ACUTE PANCREATITIS

Acute pancreatitis is generally considered an uncommon condition, however, as knowledge of this disease increases we believe that the less severe form is not unusual and is likely to be diagnosed as some more common ailment such as acute cholecystitis. Acute pancreatitis tends to occur in association with chronic disease of the biliary tract (in at least 60 per cent of cases). There may be a history of previous attacks. The symptoms vary in severity somewhat depending upon the type of process in the pancreas. Pathologically the prominent changes



occurring in various cases may be roughly classified as acute edematous, hemorrhagic, necrotic and suppurative

### Diagnosis

*Pain*—The pain of acute pancreatitis frequently follows several hours after a large meal or an alcoholic excess. It is sudden, constant, severe and originates in the epigastrium or upper abdomen and may radiate in any direction, usually it is transmitted straight through to the back. The differential diagnosis is made easier in those few instances with involvement mainly of the tail of the pancreas, where the pain is chiefly in the left side of the epigastrium, with or without radiation laterally. There is a tendency for gradual subsidence of the pain.

*Nausea and Vomiting*—These are often present and frequently to such an extent that intestinal obstruction may be simulated. Paralytic ileus occurs in the most severe cases.

*Swelling, Rigidity and Tenderness*—Rigidity and tenderness over the pancreas are likely to be present soon after the onset of pain. They are not as marked as in acute perforation of a peptic ulcer. Swelling of the epigastrium may occur and is likely to be transverse and over the area of the pancreas, tending to follow the rigidity and tenderness.

*Prostration and Shock*—The degree of prostration may be slight or absent but is usually present to some extent and may vary from actual shock and collapse to death within a period of hours. It had been thought that these patients all suffered from shock but with the increase in frequency of diagnosed pancreatitis it has become evident that this is not true.

*Leukocytosis*—The white blood cell count averages between 10,000 and 15,000 per cu mm. A count over 20,000 is usually indicative of marked peritoneal involvement or suppuration.

*Enzyme Studies*—The determination of the blood or urine amylase (diastase) is the most important and reliable laboratory procedure in the diagnosis of acute pancreatitis. The level in the blood is considered elevated when it is well over 200 mg (units). Values over 70 units for urine are significant. The rise of amylase in the first two to twenty-four hours in acute pancreatitis is so constant that its absence makes the diagnosis very unlikely. The level tends to decline after twenty-four to forty-eight hours. Determination of the level of serum lipase is im-

portant but of less value than amylase because a significant elevation may be caused by conditions other than acute pancreatitis.

*Peritoneal Fluid*—Needle aspiration of peritoneal fluid in search of free blood has been advocated as a procedure for diagnosis of the hemorrhagic type but its value does not merit its use as a routine measure

### Treatment

In the severe cases, oral intake is stopped and a suction tube is passed into the stomach. A sedative such as morphine sulfate is likely to be required in large and frequent doses for the relief of pain. Parenteral fluids should be given according to the size of the patient and the amount of vomiting, usually between 2000 and 3000 cc is administered, preferably intravenous normal saline solution containing 5 per cent glucose. About one third of these patients have a disturbance in carbohydrate metabolism and because of this some clinicians feel that the utilization of glucose should be insured by the addition of 15 to 20 units of regular insulin to each liter of glucose solution. In the event of shock, blood transfusions and plasma are indicated. Antispasmodics, such as nitroglycerin grain  $\frac{1}{400}$  (0.6 mg), have been suggested for treatment but their value is questionable and they should not be used where shock may occur.

Surgery as an emergency procedure is contraindicated except where there is reason to suspect the presence of another condition amenable to surgery, such as acute perforation of a peptic ulcer or acute appendicitis. Interval operation, after a number of days, may be indicated where there is associated biliary tract disease. At operation biliary obstruction may be relieved by cholecystostomy or the insertion of a T tube in the common bile duct. The formation of an abscess is an indication for surgical drainage.

### ACUTE APPENDICITIS

We have tended to expect the manifestations of acute appendicitis to be stereotyped. More consideration should be given to the atypical symptoms and signs, and it is important to remember that this is a disease which affects any age group. Statistics of the misdiagnoses should impress us, inasmuch as a large per-

centage of these fall in the very young and older groups. Abdominal pain of any sort should bring to mind the possibility of acute appendicitis.

### Diagnosis

*Pain*—This is the first symptom, typically beginning as a colicky, cramplike pain in the epigastric or umbilical regions and shifting to the right lower abdomen where it becomes an aching sensation. A characteristic accompaniment of pain at the onset is a sensation of fullness or tension in the rectum or colon, causing a belief that evacuation of the bowel would relieve the pain, hence the frequency of laxative taking. We wish to stress that group consisting of approximately 25 per cent of cases in which this sort of pain is not present. In the absence of appendiceal distention the early upper abdominal pain is absent. The position of the secondary localizing pain is dependent upon the extension of the inflammatory process to the peritoneum covering the appendix and the structures which surround the appendix. The pain of pelvic appendicitis may be referred to the midline or to either side of the lower abdomen. Frequently the pain from retrocecal appendicitis is localized anywhere from the outer part of the flank, behind the cecum, and at times to the upper right abdominal quadrant. The infected appendix which points toward the midline may be associated with pain referred to the left abdomen. This is especially true in children.

*Nausea and Vomiting*—It is true that these symptoms usually follow pain, but on rare occasions they may precede the pain and frequently they are absent.

*Constipation and Diarrhea*—For practical purposes these symptoms are unimportant as a rule. Too often laxatives may account for the diarrhea. In cases of pelvic appendicitis, however, the presence of diarrhea may be of diagnostic help. Constipation is no more common than in many other conditions.

*Tenderness*—This should be present in all cases. Its extent depends upon the degree to which a patient reacts to pain, the position (superficial or deep) of the appendix and the severity of the process. It is a treacherous sign unless we constantly keep in mind the above facts. We should like to stress that rectal or pelvic tenderness is important when the position of the appen-

dix is low and deep. A digital examination of the rectum is especially valuable when one is studying a child. Careful and systematic palpation in the flank is necessary if we are to find involvement of the retrocecal appendices. Too often palpation is hurried and incomplete. It should include the entire abdomen, the flanks and a rectal or a vaginal examination.

*Muscle Spasticity*—This varies from marked to mild increases in muscle tone. It may or may not be present depending to a large extent on the position of the appendix and the degree of its involvement. Its presence or absence should not confuse us if these facts are kept in mind.

*Urinary Symptoms*—Occasionally the appendix is in contact with the urinary bladder or ureter. This is especially true in children. Frequency of voiding and dysuria may occur in those instances in which the process extends by contact to the bladder. If the appendix reaches the ureter, red blood cells may be found in the microscopic examination of the urine.

*Fever*—Very early in its course, the temperature varies from normal to  $1^{\circ}$  to  $2^{\circ}$  F above normal. After the formation of pus, gangrene, perforation, or abscess, the temperature reaches various heights, depending upon the inherent resisting powers of the patient and the complication which follows.

*Leukocytosis*—Usually there is an increase in the polymorphonuclear cells, the total white count averaging from 12,000 to 18,000. On the other hand, there may be no increase, a relative increase in the polymorphonuclear cells, or the white blood count may be more than 20,000.

### Management

We would like to stress that a patient having abdominal pain should be seen at once and the typical and atypical features complained of or discovered should be carefully considered. In so doing most cases can be immediately diagnosed and treatment instituted. When there is a reasonable doubt about the diagnosis, the patient should be placed in bed, given an ice bag or hot water bottle to apply to the abdomen, sips of fluids, and if necessary to appease the family some drug such as 5 grains (0.325 gm) of sodium citrate every two hours. A review of the diagnostic problems should be made every few hours. Until a diagnosis is made, pain-relieving drugs should be avoided. After-

wards, in case the patient has agreed to surgical intervention, opiates may be administered

The proper treatment is early hospitalization and surgical intervention with or without the use of sulfonamides depending upon whether a complication has arisen prior to the proper treatment. At the present time there is no reason to believe that this newer drug therapy will supplant early operative intervention.

### ACUTE INTESTINAL OBSTRUCTION

Acute obstruction may occur in any part of the gastro-intestinal tract, but most frequently occurs in the terminal ileum. Its causes are many and include those conditions which cause obstruction in the lumen by involvement from without, such as hernia, intussusception, volvulus, adhesions and the like, conditions involving the coats of the intestines and producing obstruction such as strictures, tumors and the like, and those rarer mechanical disturbances which obstruct the lumen itself such as foreign bodies, fecal impactions and gallstones. Variations in the character of the symptoms depend upon the site of the obstruction and its cause.

#### Diagnosis

*Pain*—The pain is usually sudden in onset, at first colicky in character and later becomes continuous and is severe. The point of maximum severity is over the point of obstruction, but when an acute process is superimposed upon a chronic one, the pains are often epigastric, periumbilical, or across the lower abdomen—depending upon the site of obstruction.

*Vomiting*—Reflex emptying of the stomach tends to follow soon after the onset of pain. Gradually vomiting becomes obstructive in type with explosive, forceful emissions of mucoid, biliary green or finally fecal material (frequently after twelve to twenty-four hours) especially where the site of obstruction is below the midileum.

*Constipation*—In cases of low obstruction this may be complete, higher ones may be associated with the passage of material left below the site of obstruction. In cases of intussusception, the passage of blood has great diagnostic value.

*Shock*—A toxic protein substance is liberated from the distended injured loop of the bowel in instances where the blood

supply is interfered with. This is probably responsible for the rapid progression to shock and death in certain cases. The patient appears anxious, the skin may be clammy, the tongue dry, the pulse increases, and the blood pressure falls.

*Abdominal Signs*—In cases of high obstruction there is usually slight upper abdominal distention. When the terminal ileum is involved the distention is apt to be more central and at times the "step-ladder-like" appearance may be seen. When the colon is involved, distention is likely to be more general and at times the colon may be seen to be distended, giving the appearance of an inverted U.

By palpation one may be able to feel a herniated pouch or a distinct mass. Early, the tenderness is found over the site of the obstruction and later it is apt to become general.

In the uncomplicated cases of acute obstruction, peristaltic sounds are absent, but when obstruction is superimposed upon a chronic process, hyperactive and high-pitched tinkling sounds are heard until complete paralysis occurs.

*Blood Findings*—A leukocytosis occurs and may reach very high levels (70,000 to 80,000). The blood nitrogen increases rapidly in high obstruction and is usually normal or minimal in low obstruction. The vomiting and outpouring of fluids into the bowel is accompanied by a loss of circulating blood electrolytes, especially the chlorides, causing an alkalosis.

*Roentgenogram*—In films of the abdomen may be seen distended loops of bowel with the characteristic "feathered" or ribbed appearance of the Kerkring folds in the small intestine. Dilation over a large length of intestine may give the form of a "spiral spring." A study of films taken with the patient in the upright position may show fluid level lines surmounted by dome-shaped gas bubbles. The distended large bowel is usually peripherally placed and shows haustral markings, however, a barium enema is often necessary for differentiation.

### Treatment

Diagnostic procedures should be carried out promptly in all cases of suspected intestinal obstruction. Normal saline solution (with 2.5 to 10 per cent glucose) intravenously and transfusions of blood or plasma are necessary especially in cases of "high" intestinal and strangulation obstructions for replacement of

chlorides, to combat alkalosis and dehydration, to aid kidney function and to restore blood volume

*Surgical Intervention*—Immediate operation is indicated in all cases of obstruction by strangulation and in massive distention of the colon. In other cases decompression with the Miller-Abbott tube should be started. Wangensteen states that all cases, except those with strangulation and massive distention of the colon, should have twenty-four to thirty-six hours of decompression and then surgical intervention if the measure is unsuccessful. The danger that intestinal intubation with suction-siphonage may obscure obstruction with interference of the blood supply must be kept in mind, and cases showing a continued toxic reaction with prostration, fever, leukocytosis, and continued pain should be submitted to operation just as soon as the fluid and electrolyte balances are established.

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# OBSTETRICAL EMERGENCIES FROM THE STANDPOINT OF THE GENERAL PRACTITIONER\*

EDWARD A. SCHUMANN, M.D., F.A.C.S.†

THIS clinic is to deal with the major problems of obstetrics as they confront the general practitioner of medicine who finds his obstetrical commitments greatly augmented by reason of the war on account both of the shortage of physicians and the sharp increase in the national birth rate

The major anxiety which arises in the conduct of a maternity is the maintenance of the health of the mother and the avoidance of maternal mortality. Most causes of maternal death fall under the three main categories—toxemia, hemorrhage and sepsis—which will account for the great majorities of fatalities, all other causes combined constituting but a comparatively negligible proportion.

Happily, at least two of these disease entities have been robbed of much of their terror by modern obstetric methods, although hemorrhage still remains a serious factor.

## TOXEMIA

The mortality of eclampsia has been markedly reduced but this condition still carries with it a very definite danger to life. The greatest improvement has taken place in the lessening of the number of toxic patients as a whole and in the still greater reduction in the proportion of toxic women who go on to eclampsia. It is a most significant fact that, whereas thirty years ago eclampsia was almost always present in the maternity hospitals of Philadelphia, it is now so uncommon that many interns and residents pass their entire term of service without seeing a single case or at worst a very, very few.

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\* From the Kensington Hospital for Women and the Protestant Episcopal Hospital, Philadelphia.

† Surgeon-in-Chief, Kensington Hospital for Women, Chief of service in Gynecology and Obstetrics, Protestant Episcopal Hospital.

### Prevention of Pre-eclamptic Toxemia

This improvement in outlook may be summed up in the two words, *prenatal care*. If we except the cases of toxemia resulting from a pre-existing nephritis or hypertensive vascular disease (in which the only really successful treatment lies in the prevention of conception or the early termination of pregnancy), pre-eclamptic toxemia may be prevented in all but a very small percentage of patients.

The theories as to the etiology of this toxemia are legion but only one of them seems to fit all the facts. It is my very deep conviction that pre-eclamptic toxemia is a nutritional disease per se and that it rarely develops when pregnant women are properly fed from the early weeks of gestation. It is true that many lesions may be found in these women *after* the toxemia has begun to disclose itself. Thyroid deficiency, pituitary imbalance, placental infarcts—all of these are present singly or in combination, but they are all probably secondary to disordered nutrition.

*Diet*—Too little attention has been paid to the work of Winslow Tompkins of Philadelphia whose careful studies of many clinic patients and painstaking appraisal of the results obtained seems to fairly definitely point to the conclusion that by proper diet plus intake of certain vitamins, the occurrence of toxemia may be cut to a minimum. This diet is as follows:

#### *Morning Meal or Breakfast*

Grapefruit or an orange

One slice of bacon

One slice of whole wheat bread or toasted bread with a small amount of butter

One cup of coffee or kaffee hag

#### *Noon Meal or Luncheon*

Cold sliced ham or chicken (small portions)

One green vegetable, or instead, lettuce salad with a small amount of cheese

One slice of whole wheat bread or stale bread with a small amount of butter

One-half glass of water

#### *Evening Meal or Dinner*

Strained soup if desired

Fish, fowl, game or lamb

Two of the following vegetables: asparagus, broccoli, brussels sprouts, celery, green peas, kale, lettuce, spinach, squash, string beans, sorrel, Swiss chard, or water-cress

Bread (a small portion)

For *dessert* may take fruit, either raw or stewed (except strawberries and bananas), jello, junket, or cup custard (not sweet)

Of *fluids*, may take a half-glass of water

1 No liquid at mealtime except as indicated above

2 A glass of pure water on rising and three hours after each meal

3 A hot bath every second night on retiring, followed by active hand rubbing

4 A walk in the open air twice daily

### The Management of Pre-eclamptic Toxemia

Pre-eclamptic toxemia is manifested by a persistent rise in blood pressure, though this may be of slight degree. A continuing elevation of 15 to 20 points systolic above the norm for the woman, together with the appearance of pretibial and facial edema, an increase of weight exceeding 1 pound per week in the latter months of pregnancy and the onset of albuminuria constitute the primary signs. A sense of malaise may be present. Such signs indicate the necessity for prompt treatment. Due attention to diet, with a reduction in total food taken, the almost complete elimination of carbohydrates and sugars, but an abundance of proteins is the first step. The limitation of liquid intake to 40 ounces per twenty-four hours, and free purgation with magnesium sulfate are of great value. Bed rest, preferably hospitalization for a few days, is indicated. During this time the kidney function should be studied in detail, urea clearance tests being of great importance.

Under this plan the incipient toxemia often subsides and the evidences of its presence have disappeared after six to ten days. The patient then is permitted to resume her usual activities, reporting once weekly to her physician and maintaining a strict dietary regimen. Should the toxemia recur, the same procedures are to be repeated. Occasionally several such episodes may develop during the last four months of pregnancy and yet result in a normal accouchement at term.

Sometimes, however, the toxic signs persist and although the progress of the disease seems to be arrested, there is little or no improvement. In such instances the welfare of the infant becomes a paramount interest and it is well to induce labor as soon as may be after the period of viability of the child has been reached. Clifford and others have shown conclusively that the probability of securing a healthy baby from a toxic mother decreases almost in direct ratio to the duration of the toxemia as well as

its severity "Better a healthy premature baby than a toxic one at term"

If in spite of treatment the toxemia grows worse, and increasing edema, diminution of urine output, increase in albuminuria and in blood urea nitrogen, headache, epigastric pain and possibly albuminuric retention herald the approach of eclampsia itself, more vigorous treatment should be instituted at once. The diet is sharply reduced and consists of skim milk with an occasional bowl of purée of some green vegetable as spinach or asparagus. Purgatives with saline should be provided daily. The intravenous injection of 1000 cc. of 5 per cent glucose solution daily is of value. Should the patient evince a beginning restlessness, eclampsia is imminent and vigorous sedation is advised.

### The Treatment of Eclampsia

The treatment of eclampsia itself is based upon the following essentials

- 1 The elimination of toxins.
- 2 The control of convulsions
- 3 The maintenance of the circulation
- 4 The prevention of injury to the patient during periods of unconsciousness
- 5 The preservation of the life of the child if possible
- 6 The prevention of permanent damage to the kidneys

Happily, most patients in eclampsia go into labor spontaneously, this being Nature's method of eliminating the source of the toxemia. In those who do not develop uterine contraction, induction of labor by rupture of the membranes or the insertion of bougies is feasible, but not in the case of primigravida with long canalized cervixes and no effacement. Surgical methods of procuring delivery, as accouchement forcé, are inadvisable because the eclamptic woman withstands trauma badly.

The elimination of toxins is aided by free purgation by copious colonic lavage using large quantities of water and sometimes by sweating by means of the hot dry pack followed by careful toweling to dryness and a complete change of bed clothing.

For sedation a modification of Stroganoff's technic is employed in these clinics. Magnesium sulfate, 20 cc. of a 10 per cent solution, is administered intravenously at four-hour inter-

vals, not more than 10 cc of the salt being given in twenty-four hours

Morphine sulfate, grain  $\frac{1}{4}$  hypodermically, is exhibited at intervals of from one to four hours, depending upon the reaction of the patient. A respiratory rate of 12 per minute and/or a pulse rate of 60 or below reveals that the therapeutic limit of morphine has been reached and the drug must be discontinued until elimination takes place. Phenobarbital in doses of from 6 to 10 grains is a useful adjunct to the morphine.

Every care must be taken that the patient in convulsions may suffer no injury. A padded spoon handle or tongue depressor kept between the teeth will prevent tongue or cheek biting. Restraint by sheets may save an injury from a fall from the bed and whenever possible the crib type bed should be used.

As soon as she can swallow, the patient is given water freely and the parenteral use of fluids is advised. Failing circulation is supported by digitalis which also acts as a diuretic. In a florid woman with great general congestion and a laboring right heart, venesection with the withdrawal of 1000 cc of blood often is of great benefit.

During the entire course of the eclamptic attack, the patient should be kept in a quiet, semidarkened room and carefully protected from chilling.

Ordinarily, such a course of treatment will be followed by a gradual cessation of convulsions, return to consciousness, and an increased urine output. Somewhere during the attack labor and delivery have usually taken place and improvement thereafter is rapid.

*The Place of Cesarean Section in Eclampsia*—Speaking generally, cesarean section, or indeed, any major operative procedure has no place in the management of eclampsia. However, there are some women who do not improve at all under the conservative treatment as outlined above, and in whom vaginal delivery is impracticable by reason of the undilated and uneffaced cervix, cephalopelvic disproportion, or other causes. Here I feel that cesarean section has a distinct place and the operation when performed under local anesthesia sometimes is responsible for the recovery of a woman in whom all other phases of treatment have failed. Such cases are few and the writer insists that he does not advocate abdominal hysterotomy as a treatment.

for eclampsia per se, but only employs it when all other measures have failed

*The Subsequent Management of Eclamptic Women*—Close and persistent follow-up observation is necessary in all cases. Many patients recover completely, blood pressure, weight, urine all becoming normal within a few weeks. These women may be dismissed with the advice that they avoid pregnancy for at least one year, and should conception occur they should at once place themselves under the care of a competent physician, informing him of their previous toxic episode.

Those patients who do not recover and in whom there are evidences of permanent kidney damage or vascular disease in general, should be advised to consult an internist at once and be guided by his advice as to their future.

#### THE HEMORRHAGE OF PREGNANCY

The etiology of bleeding during pregnancy varies with the period of gestation and, for the purpose of diagnosis, it is well to consider pregnancy in its three trimesters and to classify the causes of hemorrhage in each according to their relative frequency.

In the first three months, by far the most common cause of uterine bleeding is threatened or inevitable abortion, the second is ectopic pregnancy. These two account for more than four fifths of all hemorrhages. Next in point of frequency are hydatidiform mole, persistence of menstruation, menstruation from one horn of a double uterus, uterine polyps and cervical erosion or carcinoma, all of which are uncommon.

#### Differential Diagnosis of Threatened Abortion and Ectopic Pregnancy

Although the classical picture of abortion shows pain, hemorrhage and dilatation of the os, it is noteworthy that in many instances painless bleeding may persist for several weeks, before complete separation of the ovum, or its death inaugurates uterine contraction with the development of the other two elements of the syndrome.

Hemorrhage in abortion may be furious, with rapid exsanguination of the patient, but I have never yet seen a fatality from this accident which could be ascribed to hemorrhage alone. When infection occurs, the prognosis among women with severe

anemia becomes very grave, but bleeding without infection is rarely a cause of death

The diagnosis of abortion with hemorrhage may be made by the elicitation of the signs and symptoms of pregnancy in the first trimester plus the findings of some degree of dilatation of the cervix on bimanual examination and the history of pain and bleeding. If fragments of decidua or placenta are found, the evidence is conclusive. The most important condition with which uterine abortion may be confused is ectopic pregnancy and the differentiation of these conditions is often difficult.

The classical picture of ruptured ectopic pregnancy—sudden, catastrophic pain, with fainting and collapse—is seen in slightly less than half of all cases, the more common symptoms being a dull but increasing abdominal pain, rigidity of the recti muscles, slight elevation of temperature and a moderate or high leukocytosis. Associated with these symptoms is vaginal hemorrhage, which although it may at times be fairly profuse, is never violent. Indeed, one of the valuable signs for differentiation is the fact that the woman suffering from ectopic pregnancy may, and frequently does, show the effect of severe blood loss, although the visible hemorrhage is negligible, whereas in intra-uterine abortion, the evidence of anemia is in direct ratio to the visible amount of blood.

The history in these cases is also most important from a diagnostic standpoint. In abortion, there is complete amenorrhea, with the associated subjective signs of pregnancy—nausea and vomiting, polyuria, pain and tingling in the breasts and increased vaginal secretion. In ectopic pregnancy the signs of pregnancy are vague, usually—at least not so pronounced as in uterine gestation. The amenorrhea is generally not complete. The patient will state that she has missed a period, but noted some slight spotting a week or two later, which has been repeated in greater amount before the onset of pain.

On bimanual examination, the uterus in abortion is definitely increased in size, is soft and globular in outline. The cervix is velvety and dilated to a varying extent. There may be some cyanosis of the cervical and vaginal mucosa, and Hegar's sign—obliteration of the lower uterine segment—may be present. Ladin's sign, a small area of marked softening in the anterior wall of the cervix and lower uterine segment, is a common find-

ing In ectopic pregnancy, the uterus is generally only slightly enlarged and the characteristic boggy density is not noted. Movement of the cervix is often quite painful, and palpation of the adnexa may or may not reveal the presence of a tender, soft, spindle-shaped mass. If there has been a considerable accumulation of blood in the pelvic cavity, the cul-de-sac may bulge, with a doughy sensation being imparted to the examining finger.

The nature of the pain in the two conditions is often very valuable in diagnosis. In abortion the pain is intermittent, cramp-like, and the patient likens it either to menstrual cramps or labor pains. In ectopic pregnancy the pain is at first to one side or the other of the midline and then becomes a generalized abdominal ache, as free blood in the peritoneal cavity causes irritation and mechanical peritonitis.

#### Management of Abortion with Hemorrhage

The management of abortion with severe hemorrhage is usually restricted to packing the vagina firmly with gauze or cotton, under aseptic precautions, the packing to remain in place for twenty-four hours, after which the products of conception will often be found lying free in the vagina, upon the removal of the gauze. When the abortion occurs at the end of the third month, or early in the fourth, the placenta may often be found lying in the cervical canal and presenting as a tightly rolled cylinder, simple extraction with the fingers or a ring forceps, in this circumstance, often stops the bleeding. The administration of ergot, especially the newer ergonovine preparations, will do much to contract the uterus and aid the extrusion of the ovum. If fever is present, the sulfa drugs should be administered.

Curettage is not often necessary, although it may be required in the presence of persistent bleeding. Although this is a minor operation it requires considerable skill and care, for perforation of the pregnant or puerperal uterus is by no means an uncommon accident.

#### Management of Ectopic Pregnancy

The management of ectopic pregnancy requires little comment. Prompt laparotomy upon the establishment of the diagnosis is the rule. One point of importance is that, in the interval between the occurrence of the hemorrhage and operation, there



should be no stimulation or intravenous therapy practiced Morphine to secure rest, elevation of the foot of the bed, and external heat are valuable measures, but stimulation should be reserved until the patient is prepared for section, when blood transfusion, 10 per cent glucose intravenously and cardiac stimulants may be used freely.

### Hydatidiform Mole

Hydatidiform mole is a somewhat uncommon, but very definite, source of uterine hemorrhage. The *diagnosis* may be confirmed by the fact that the uterus is considerably larger than normal for the duration of the pregnancy, that the patient has experienced more than the ordinary degree of nausea and vomiting, that the Aschheim-Zondek or Friedman test is positive with greatly diluted urine (one tenth the usual amount) and that, if the pregnancy be of more than sixteen weeks' duration, roentgenologic examination will fail to show centers of fetal ossification. The passage of the little cysts which constitute hydatidiform mole is conclusive evidence.

The *treatment* of mole is immediate removal of the growth, per vaginam possibly, but better by abdominal hysterotomy under local anesthesia, the mole being removed under vision. It is almost needless to say that all such cases should be closely watched, with periodic Friedman tests, to determine the possible signal of chorionepithelioma.

The other causes of bleeding during the first three months which I have mentioned are uncommon and may usually be recognized with ease by a speculum examination.

In the second trimester, abortions still take the lead as a cause of hemorrhage, closely followed, as this period draws to a close, by the bleeding from placenta praevia. Ectopic pregnancy, polyps and so forth may be responsible, but not commonly so, since their presence has been usually disclosed earlier.

### Placenta Praevia

*Diagnosis*—After the fifth month, placenta praevia must always be uppermost in the mind of the obstetrician when uterine bleeding is present. Here the classic symptom is painless bleeding, often slight in amount at the first attack, with irregularly recurring hemorrhages of increasing severity. The diag-

nosis of placenta praevia so early in pregnancy offers great difficulty. Since endometritis is an etiologic factor, a history of preceding abortions or uterine disease is of some value. The condition occurs far more commonly in multiparas than in primiparas, and the bleeding is always painless, and seemingly without cause, although coitus or excessive muscular exercise may precipitate a hemorrhage.

When there is grave doubt, the *roentgenologic method* of diagnosis as described by Ude and Urner is of great value. Their technic is to instill into the empty bladder about 40 cc. of a solution of sodium iodide (12.5 per cent) or other contrast material. An anteroposterior film of the pelvis is now made, the catheter having been first withdrawn. In normal pregnancy, the presenting head lies almost in contact with the bladder, the intervening space occupied by the lower uterine segment, the space between bladder margin and fetal head appearing to be about 6 to 8 mm. in length. In placenta praevia, the mass of the placenta, its concave border upward, lies between the fetal head and the bladder, separating the two by a space of varying width, depending upon the thickness and location of the placenta, and clearly visible on the x-ray film. This method constitutes a distinct advance in the diagnosis of placenta praevia, especially because it involves no vaginal manipulation, which might favor separation or lead to infection. The soft tissue x-ray which discloses the location of the placenta, especially upon the lateral view, is of great value in diagnosis.

Lacking roentgenologic facilities, the diagnosis must depend upon the history, the nature of the bleeding, and auscultation with possible demonstration of a placental bruit low over the symphysis. The discovery, upon vaginal examination, of a soft doughy mass lying between the head and the cervix will confirm the diagnosis, but this is a dangerous maneuver and should not be undertaken unless the accoucheur is prepared to deal at once with dangerous hemorrhage.

*Treatment*—The treatment of placenta praevia constitutes one of the major problems of obstetrics and the management of this lesion before the complete viability of the child is a very perplexing one. It has been well said that there is no expectant treatment of placenta praevia, and one or two bitter experiences with attempts to temporize in such situations have amply con-

vinced me of the correctness of this axiom. What is to be done with the young woman, a primipara, let us say, who is in the seventh month of her pregnancy, ardently desires a child, and develops the characteristic signs of placenta praevia? It is true that in many instances a tranquil life, avoidance of coitus, vigorous exercise and the use of cathartics will allow pregnancy to continue to term or nearly so, without serious hemorrhage. It is also true that such patients may suffer a tremendous blood loss, of dangerous or even fatal volume, at any moment, bleeding sometimes occurring during sleep. Nor is there any procedure available by which such accident may be forecast.

It follows then that pregnancy should be terminated as soon as the diagnosis is made, either by abdominal hysterotomy, or by induction of labor, depending upon the degree to which the placental mass covers the cervical canal. On the other hand, the desire to conserve the life of the infant, religious objections, and the fact that pregnancy may continue without disturbance render such radical treatment quite distasteful, so that I have come to the conclusion that the best plan available is to explain the situation to both parents in great detail, and to require that the final decision come from them. For the protection of the physician against future criticism, should disaster follow conservative management, it is well to have the prospective mother and father state their wish in writing.

When the first hemorrhage occurs after the child is viable, a different problem arises. Undoubtedly, the best prognosis to mother and infant is offered by cesarean section, preferably of the classical type, performed under local anesthesia by one fully trained in major obstetric surgery and in a qualified hospital. This applies to all cases, except those occurring in multiparas with partial placenta praevia, where there is an available area of the cervical canal occupied by the membranes alone, thus permitting the induction of labor by simple rupture of the membranes or by the insertion of a dilating bag. As my own experience grows, I find myself rarely regretting the decision to deliver by section, while sometimes wishing this method had been chosen rather than the finally selected vaginal route.

In those emergency cases wherein the obstetrician is faced with the problem of serious hemorrhage with beginning labor, in a locality where prompt and efficient section is not available, the matter is serious indeed. Here there are several procedures

available, none of them quite satisfactory but necessary as emergency measures. They are as follows: simple rupture of the membranes with the use of small doses of pituitrin, subcutaneously or by the nasal route, Braxton-Hicks version, the use of the metreurynter or dilating bag, and as a last resort, vaginal packing together with the use of a tight abdominal binder.

Simple rupture of the membranes, the Rotunda method, sometimes permits the descent of the head to act as a tampon and, when combined with pituitrin to maintain uterine contraction, is of much value.

The Braxton-Hicks version—turning the child and drawing down a leg until the buttocks make pressure upon the placenta—works well for the mother but is extremely hazardous for the child, and is not available unless there be sufficient cervical dilatation to permit the entrance of two fingers into the uterine cavity. It should be remembered that extraction of the infant after this type of version is dangerous and that delivery should be left to the forces of nature insofar as possible.

The use of the dilating bag was strongly advised by the late Dr. Cragin, who achieved great success with this treatment. The folded and lubricated bag should be passed alongside of the placenta if this be possible, or should be plunged through the mass of that organ if the praevia is central. The violent hemorrhage excited by perforation of the placenta is dealt with by rapidly filling the bag to capacity with an antiseptic solution and attaching a weight to the tube to insure strong pressure against the placenta from above.

Vaginal packing is a last resort, as has been said. If hospital facilities are not available, if the cervix is elongated and undilated and the hemorrhage furious, it is proper to pack the vagina fully and firmly, using due precautions as to asepsis, and then to apply a very tight abdominal binder. This plan may serve to compress the placental site between the packing below and the uterus which has been forced down from above, and is a device which, while not generally advised, may be life-saving if no better plan of treatment offers.

#### **Abruptio Placentae**

In the last trimester, placenta praevia and abruptio placentae are the chief causes of uterine bleeding. Abruptio placentae, which is a premature separation of the normally implanted

placenta, is a somewhat uncommon accident which may rarely arise as a result of trauma, more frequently is said to be due to some form of toxemia, but often occurs without demonstrable evidences of such toxemia or even of degenerative changes in the placenta itself.

This accident, the concealed hemorrhage of the older writers, usually occurs during the last month of pregnancy, sometimes earlier. It is characterized by hemorrhage, not necessarily great in visible amount, but always associated with pain, more or less severe in type.

The separation usually takes place suddenly, the woman experiencing a sharp, lower abdominal pain, which steadily increases. The uterus becomes hard, often described as ligneous, and is tender to palpation, the fundus becoming flatter and broader. Fetal movements and heart sounds disappear and a trickle of blood escapes between the membranes and the uterine wall and appears at the vulva.

If the separation is extensive, the evidences of internal hemorrhage develop rapidly, the air hunger, leaking skin, pallor and falling blood pressure attesting to the profound anemia. As the separation becomes more nearly complete, the presence of blood in the uterus may force a large vaginal bleeding with many clots. *Abruptio placentae* is a matter of grave moment, both maternal and fetal mortality being exceedingly high.

The only available *treatment* is immediate delivery, per vaginam, if happily the cervix is sufficiently dilated to permit of forceps extraction, or abdominal hysterotomy. In the latter case, the uterus is often so infiltrated with blood that hysterectomy becomes necessary.

## COMPLICATIONS OF THE THIRD STAGE OF LABOR

### Retained Placenta

If the placenta has not been expelled thirty minutes after the birth of the child it is said to be retained. The first step in securing delivery of such placenta is the Credé maneuver. This consists of grasping the fundus uteri through the abdominal wall with both hands and making rhythmical, gentle but firm pressure, in an attempt to reduce the volume of the uterus and so compel it as to dislodge the placenta and force it through the cervix.

The pressure should never be rough and should never be continued more than ten minutes, five is better. In the intervals between pressure, the fundus may be gently massaged with a circular motion in order to stimulate the muscle fibers to contract.

Credé expulsion failing, the next step is manual extraction of the placenta. For this purpose the patient, usually still somewhat under the influence of a sedative (nitrous oxide anesthesia is occasionally necessary), is replaced in stirrups, rescrubbed and redraped. The operator is also scrubbed.

INVASION OF THE UTERUS AFTER DELIVERY IS MORE DANGEROUS THAN BEFORE, SINCE THE ENTIRE INTERNAL CAVITY HAS BEEN CONVERTED INTO ONE GREAT SUPERFICIAL WOUND.

With meticulous asepsis the hand is introduced into the vagina. The cervix may be contracted and the detached placenta simply incarcerated within the uterus. In such cases, the cervix may be gently dilated with the fingers and the placenta withdrawn, continued pressure being made on the fundus by an assistant. (This accident is very rare in our experience.)

Generally the cervix easily admits the fingers which then feel the margin of the placenta, and being inserted beneath it, gently, with a sort of wiggling motion, peel the placenta from the uterine wall. Sometimes only a portion of the organ is adherent, sometimes the entire area. The placental site is palpated for remaining fragments which are pinched off with the finger or removed with placental forceps if this be required. Often there is free bleeding after an adherent placenta has been delivered, and packing should be used without hesitation. Four grams of sulfathiazole introduced into the uterus with the packing tends to inhibit the development of sepsis.

*Placenta Accreta*—Rarely there is such intimate connection between placenta and uterine wall that no line of cleavage can be palpated and the organ will not peel off the uterus. When this is discovered all attempts at manual removal must cease at once, and the uterus packed with gauze after the instillation of sulfathiazole, the cord ligated close to the vulva and cut. The subsequent treatment may be hysterotomy or expectancy, this to be determined later. All patients with retained placenta should be specially observed for twelve hours after delivery, as late hemorrhage is not infrequent.

### Postpartum Hemorrhage

There are two common varieties of postpartum hemorrhage. One consists of massive bleeding immediately after the third stage of labor, which is very alarming but not too dangerous because immediate active treatment is always instituted. The other is a mild bleeding which is not alarming but which does not quite cease. Some hours pass, nurses and physicians go off duty and the newcomers are not aware of the amount of blood loss which the patient has suffered. Suddenly there is collapse and death from hemorrhage, although at no time has there been any severe bleeding.

To prevent this accident it is a rule of the service that in cases of postpartum hemorrhage the physician who conducted the delivery is solely responsible for the patient until the bleeding has definitely ceased.

*Treatment of Postpartum Hemorrhage*—Haste, packing and transfusion are the essentials of treatment. The moment the obstetrician feels that undue bleeding is occurring he should begin treatment as follows:

One ampule of ergonovine or another of the newer ergot alkaloids is injected intravenously.

The fundus uteri is firmly grasped through the abdominal wall, one hand behind the fundus and one in front. The uterus is then strongly compressed and at the same time pulled upward and forward. After five minutes the bleeding may have greatly lessened and the pressure may be relaxed, the uterus being continually palpated to discover relaxation.

If bleeding persists, the patient is placed in stirrups, scrubbed and draped and the prepared operator examines the cervix, single speculum and ring forceps being used to grasp the lips of the organ. Should the bleeding arise from a laceration of the cervix, this is repaired with interrupted catgut sutures.

If the cervix is not the source of the hemorrhage the uterus must be firmly packed with gauze packing  $2\frac{1}{2}$  inches wide and using four thicknesses of gauze. The packing is best introduced with the fingers, care being taken to pay out the gauze over a forceps held by an assistant so that it is not contaminated by rubbing against the labia.

The uterus is packed until the thrust of the fingers is clearly felt by an assistant with hand palpating the fundus through the

abdominal wall and until no more packing can be introduced. If the fingers do not suffice, a packing forceps may be used but in this event great care must be exercised lest the forceps perforate the soft uterus.

Should the bleeding persist and soak through the packing, the latter should be withdrawn, clots wiped out of the uterine cavity and the packing replaced even more firmly than before (under aseptic precautions, of course). Sulfathiazole, 4 gm., may be introduced with the packing. While this is proceeding, preparations for blood transfusion or plasma injection are going forward so that the transfusion may be started even while the uterus is being packed or as soon thereafter as may be. Glucose in saline may be used if blood is not immediately available. Heart stimulation, lowering of the head of the bed, application of external heat and other supportive treatments are carried out.

Ergonovine is exhibited hypodermically every four hours for two or three doses. If all goes well the packing may be removed in twenty-four hours.

If, in spite of these measures, bleeding continues and the patient's condition becomes desperate, hysterectomy may be imperative.

#### GENERAL MEASURES

General measures have not been mentioned previously in the management of the hemorrhages of pregnancy and labor because these measures are used in the same manner in all cases of excessive bleeding.

Modern obstetrics demands that in every case of uterine bleeding blood transfusion must be immediately available. The securing of blood donors, then proper matching and typing, should run parallel to the first evidence of abnormal bleeding. Blood should be used freely and abundantly and plasma must also always be on hand.

The parenteral installation of supportive fluids such as 5 per cent glucose in saline is a most important adjuvant in the treatment.

#### PUERPERAL SEPSIS

This dreaded complication of labor has happily lost much of its terror since the sulfa group of drugs has come into common use, but even with this great advance, sepsis still remains one of the great causes of maternal death.



The prophylaxis against sepsis—the meticulous care in preparing the patient for delivery, the reduction of vaginal examinations to an absolute minimum and their conduct under the most scrupulous aseptic technic, the avoidance of contamination during delivery, especially if this be operative in nature, the aseptic technic of the puerperium—all of these are so well known to the profession that further discussion is unnecessary here. Suffice it to say that once the significant chill and febrile temperature have appeared, in spite of all precautions the most unremitting care in both diagnosis and treatment is required if the patient's life is to be saved.

*Prompt diagnosis* is a *sine qua non*. Pyelitis must be eliminated by frequent examination of catheterized specimens of urine, the upper respiratory tract must be studied to discover a possible lesion and extraneous inflammatory foci such as appendicitis and cholecystitis must be ruled out as must be the exanthemas.

When the diagnosis becomes apparent the treatment may be epitomized as follows (in hospital practice the patient has been isolated upon the first appearance of pyrexia)

- 1 Repeated blood transfusions consisting of 200 cc of citrated blood daily or 300 cc every other day, or plasma in similar amounts. Should there be a reaction of any degree after blood transfusion the Rh factor in the blood must be investigated.
- 2 Sufathiazole or sulfadiazine 4 to 8 gm in twenty-four hours by mouth, guarded by daily estimation of the drug blood level.
- 3 Maintenance of fluid balance by intravenous injections of 5 per cent glucose in normal saline, at least 1000 cc in twenty-four hours.
- 4 Relief of pain and securing of rest by use of barbiturates, or by morphine if necessary.
- 5 Bowels moved by enemas.
- 6 Light diet.
- 7 Postural change, external heat and similar measures to promote bodily comfort.
- 8 Repeated blood cultures to determine course of the disease.
- 9 Regular pelvic examination to discover localized collections of pus, which when found should be drained promptly.

Extensive operative procedures such as hysterectomy and ligation of the veins of the broad ligament are not advised

It is essential that a septic patient be kept at rest until the temperature has been normal for at least three days, the leukocyte count again reaches the norm, and the sedimentation rate has lost its sharp curve. Failure to observe this rule too frequently results in disaster from pulmonary or cerebral embolism.

Many more complications of maternal care confront the practitioner, which may not be considered here for lack of space. Dystocia in its varied forms, rupture of the uterus, inertia uteri and severe lacerations are constant attendants upon an obstetric practice, but all can be successfully managed by careful study of the condition and its prompt treatment. Care in observation and a thoughtful weighing of symptoms and signs are the keynote of success.

## ACUTE ENDOCRINE DISTURBANCES

CHARLES WILLIAM DUNN, M.D., F.A.C.P.\*

ACUTE or emergency phases are seldom seen in many endocrine disturbances, but there are a limited number, such as Simmonds' and Addison's diseases and parathyroid tetany, in which the clinical picture is frequently associated with acute or emergency states requiring prompt and active therapeutic intervention in order to prevent a fatal outcome. Indeed, there are those who hold that in spite of therapy every case of Simmonds' disease has a fatal prognosis.

The fact that the more common endocrine disorders seldom present acute phases does not relieve us from appreciating the possibility of an emergency or acute state arising during the course of a presumably chronic endocrine state. It is therefore required that the internist, the neurologist and even the surgeon as well as the endocrinologist be mindful of the fact that occasionally a patient with a chronic form of endocrine disease can develop an acute clinical state which can mimic a classical syndrome for which they would ordinarily advise emergency operative therapy. Acute endocrine disturbances are consequently important from both a diagnostic and a therapeutic viewpoint.

There is another aspect of acute endocrine disturbances which has received all too little attention, namely, the exaggerated physiological and/or toxic effects which can occur following the administration of many therapeutic agents of the endocrine group. The possibility of the production of these effects is becoming all the more evident as the utilization of endocrine preparations becomes more general. In fact, the introduction of synthetic chemical products possessing definable hormonal action, in spite of the fact they are not known body

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\* Associate in Medicine, Graduate School of Medicine, University of Pennsylvania, Endocrinologist, Graduate Hospital of the University of Pennsylvania and Abington Memorial Hospital

constituents or its products, intensifies the need for recognizing this danger in endocrine therapy

#### THE HORMONES IN THE MAINTENANCE OF CHEMICAL BALANCE

When an acute phase occurs in an endocrine disturbance, the underlying factor responsible for the critical or serious condition of the patient is usually a disturbance in his blood chemistry. The hormones were originally described or defined as chemical regulators by Claude Bernard in 1891. If we exclude the biological activity of the hormones on the tissue processes concerned in growth and sexual development and their respective physiological maintenance—however, even in these developmental processes, hormonal chemical processes and their regulation are operating as an essential factor—we must agree that the hormones most important in the maintenance of physiological balances are of chemical nature. It is of utmost importance to the therapist and also the diagnostician to recognize this fact. The therapist must promptly correct the abnormal chemical balance in the blood during an acute endocrine state by intravenous or a less rapid method of administration of the deficient blood chemical or chemicals, and then maintain the chemical balance at normal by administering the hormone or hormones which affect the metabolic control of these chemicals, and he must also exclude from the diet those foods which contain the chemical substances opposing the action of the deficient blood chemical and which have risen to above normal values during the deficiency period.

For example, the action of potassium in the body is opposed to that of sodium, and a similar relationship exists between phosphorus and calcium. Therefore, in endocrine disorders in which a deficiency of sodium or calcium occurs we eliminate, respectively, potassium or phosphorus. By recognizing the dietary factors of the disorder we not only aid the patient's recovery and enhance his ability to establish normal blood chemical balance, but equally we diminish the requirements of hormone in the subsequent maintenance period. This principle of the reduction of the intake of foods containing the chemical that opposes the effect of the chemical found deficient in the endocrine disorder in question has been one of the great advancements in the management of endocrine disorders and

particularly of those cases in which there is a tendency for acute endocrine states to appear or recur

Now it may be asked "If the pituitary hormones, the adrenal cortical hormone, the androgens and the estrogens individually or collectively are concerned in maintaining the same single or combination of chemicals at normal levels in the blood, why, for example, do not all anterior pituitary deficiency states present in principle the abnormalities in blood chemistry observed in Simmonds' disease?" The explanation appears to be that Simmonds' disease represents a major deficiency in anterior pituitary function and that all other anterior pituitary deficiencies are less pronounced and thus do not present the same degree of disturbance in the interrelationships of the endocrine glands that is present in Simmonds' disease. The trophic factors of the anterior lobe normally stimulate the other members of the interrelated endocrinous system. In most instances of anterior pituitary deficiency one of the other endocrine glands takes on an increased role in the regulation of a chemical substance controlled by the anterior pituitary, thereby offsetting the effects of the primary anterior deficiency. In Simmonds' disease, however, we have essentially a "pan" deficiency of the trophic factors of the anterior lobe. The supplemental physiological activity of a gland (thyroid, adrenal cortex, gonads, parathyroid) associated in the control of the blood chemical becomes impossible because it is also atrophied along with the anterior lobe, and the deficiency of endocrine function is therefore a general one and on a parallel plane.

The same explanation may be offered for the infrequent acute episodes which occur in the more chronic or nonprogressive anterior pituitary deficiencies. For some unpredictable or unexplainable reason the supplemental augmented physiological activity of a cooperating hormonal mechanism may fail to maintain itself, and an acute phase occurs in an anterior pituitary deficiency disorder which usually seldom exhibits an acute or emergency state.

The extent of the chemical deficiency in the blood will naturally be directly proportionate to the degree of the deficiency of the one or more hormonal factors concerned in the blood chemical dysbalance. We are not alone combating a deficiency of an inorganic chemical such as sodium, chlorides or

calcium but a chemical dysbalance, for as the one inorganic chemical element in the blood falls in content its opposing inorganic chemical element rises in the blood. An exception is blood sugar (glucose), which is lowered as the result of a deficiency of the hormonal factors that bring it into the blood to offset the effect of insulin. The normal values of glucose in the blood are maintained by hormonal factors which are physiologically opposed. The pancreas produces insulin which consumes the glucose in the blood, thus lowering the blood sugar content. The lowering of the level of the blood sugar stimulates into activity those hormonal forces which mobilize blood sugar from the glucose storage depots, namely the diabetogenic factor of the anterior lobe, the adrenal cortical hormone, adrenalin from the adrenal medulla, and possibly pituitrin, and there is some evidence of an indirect action by the sex hormones. Co-operating with these hormonal mechanisms are nervous controls acting directly on sugar metabolism and indirectly through the endocrine mechanism. For these mechanisms to operate normally, liver function must be normal and muscular storage of glycogen must likewise be functioning.

#### HYPOGLYCEMIC CRISES IN ENDOCRINE DISORDERS

Disturbances of carbohydrate metabolism and blood sugar content account for most of the acute endocrine clinical states. Exclusive of diabetes, all of these acute conditions are associated with depressed blood sugar levels. The state of hypoglycemia may be due to a deficiency of function of either the anterior pituitary or of the adrenal cortex, or it may result from hyperinsulinism. In all cases it is the action of the insulin which produces the hypoglycemic state. In pituitary and adrenal cortical deficiency overproduction of insulin is not present, but normal insulin production by the pancreas is unopposed by the respective glands. In hyperinsulinism, a normal amount of blood sugar elevating fraction is being produced by the anterior pituitary and the adrenal cortex, but due to the presence of an adenoma of islet cells of the pancreas an increased amount of insulin is being produced and the blood sugar is reduced to sub-normal levels. It is therefore evident that with the finding of a low blood sugar or hypoglycemia we cannot arrive at a complete endocrine diagnosis or the method of therapy.

The diagnosis of hypoglycemia from the symptoms alone often presents difficulties. One has but to recall that most of the earliest cases of pancreatic adenomas were found in a mental hospital and that surgical extirpation of the adenoma cured these incorrectly diagnosed mental cases. This is one illustration of the necessity for the neurologist and psychiatrist to give a guarded diagnosis is the case of a mentally agitated patient whose mental episodes have been ushered in by an acute precipitant phase. Neurological manifestations in hypoglycemia may range from precipitant (no aura) convulsions or coma, attacks of amnesia or temporary disorientation, nervousness, restlessness, headaches and abnormal behaviorism, of unexplained origin, to complex syndromes of neuroagitated states with weakness and asthenia. Many hypoglycemic patients complain of sleeplessness and restlessness, palpitation, vague and widely diversified atypical pains, sweating, lack of concentration, temperamental outbursts, dizziness, swooning and mental lapses. In a measure the failure to explain the symptoms by any sound clinical interpretation should suggest the possibility of the presence of a hypoglycemic state, especially if the patient is to all outward appearances otherwise healthy in mind and body.

Unfortunately in hypoglycemia a low blood sugar level cannot always be demonstrated by a single sugar tolerance test or the four-hour curve. Very often it is necessary to make one or more six-hour curves to obtain an accurate hypoglycemic level. In other instances an insulin tolerance test is necessary to establish the insulin sensitivity of the patient. The insulin tolerance test is made by giving  $\frac{1}{10}$  unit of insulin per kilogram of body weight. Whenever this test is given in a questionable case of Simmonds' disease, a 10 per cent glucose solution should be available for intravenous administration in the event a convulsion or coma is precipitated during the administration of the insulin.

The hypoglycemic patient may develop symptoms which are characteristic of the acute abdomen, particularly of appendicitis and gastric or duodenal ulcer which may even appear to be of the ruptured type. Gallbladder disease may also be simulated. One of our patients, a male aged eighteen years, had an emergency operation for appendicitis, and a normal appendix was removed. Six weeks later his symptoms were those of acute duodenal ulcer. The corrected diagnosis was eunuchoidism and

**hypoglycemia** Another patient, a woman aged twenty-four years with hypoglycemia, had a series of operations which started at age eighteen years with a dilatation and curettage for dysmenorrhea, which was followed at yearly intervals by appendectomy, thyroidectomy, oophorectomy, gastro-enterostomy, resection of gastro-enterostomy, cholecystostomy. None of these surgical procedures relieved her complex symptoms after the periods of postoperative care and recuperation had passed. During these periods her inactivity and dietary intake would adequately maintain her blood sugar. As soon as activity was resumed her carbohydrate metabolism again broke down and the symptom complexes which had simulated the accredited indications for her surgery recurred in part or in entirety. In fact the patient was referred to determine whether or not total castration was indicated. Her case illustrates the variety of surgical states under which hypoglycemia can masquerade and, more important, the unreliability of the four-hour sugar tolerance test even when repeated at frequent intervals. It required six-hour tolerance tests to demonstrate her hypoglycemic reactions.

Just as the patient with Addison's disease has an abnormal desire for salt and obtains a sense of improvement from its use, so does the hypoglycemic patient have an increased desire for sugar products, particularly within three hours after a meal or late at night. Likewise he obtains relief or amelioration of the acute or distressing symptoms following the ingestion of sugar. In other words, the diagnosis of the hypoglycemic state is initiated by the *history* of the patient. The importance of the history cannot be too forcefully stressed, as is well illustrated in the following case.

A male, aged thirty years, a recent college graduate and former college varsity football player, was diagnosed as having essential hypertension and diabetes. He complained of nervousness, palpitation, periods of weakness and exhaustion, profuse sweating, fatigue, falling asleep while reading a paper, in fact an almost constant tendency to drowse off during non-sleeping hours. He had changed, adversely, from a temperamental aspect. His mental output and energy were unfavorably affected. His physique and outward appearance was that of a varsity athlete. His complete physical examination had been reported to him as negative except for hyper-



tension, the blood pressure being 150 systolic and 90 diastolic, a sugar tolerance test of the diabetic type. He stated that he received a series of x-ray treatments to his adrenal gland for hypertension, a diabetic diet and 20 units of insulin daily. At end of two months his symptoms had not improved, in fact they were aggravated and he was now unable to work because of pituitary, nervousness, profuse sweating, weakness, somnolence, dizziness. Furthermore, he had become mentally morbid and his temperamental outbreaks and disinterest in home and the constant tendency to fall asleep made him intolerable to his recent bride.

The history of the patient, taken in detail prior to the aforementioned diagnosis, clearly revealed two facts: he had an abnormal desire for sugars, obtained temporary relief of his symptoms by ingestion of sugar and felt exceptionally well when alcoholic beverages were taken, and he had failed to gain weight in spite of discontinuance of training and varsity football. The immediate history revealed that his symptoms were aggravated in intensity, their complexity and duration were increased by the diabetic and insulin. In fact, he voluntarily discontinued insulin because of the reactions it induced and its intensification of his hunger for sweets with an inability to obtain the relief he formerly experienced. With a six-hour sugar tolerance test 60 mg. of sugar were found in the blood at two and four hours, and because of increasing symptoms of a hypoglycemic nature at the fifth hour glucose was orally administered and the symptoms relieved.

This patient when first examined was in an acute agitated mental state which could only be considered as being mixed with fears and despair. He was assured that he did not have diabetes and that his hypertension could be explained on the basis of a physiological reaction of the body to correct his hypoglycemia. With the proper dietary management, nourishment between meals, increasing the carbohydrate and fat content of his main meals and moderate exercise as walking after his evening meal, this patient promptly responded to his dietary therapy. Dietary management should first be explored before endocrine therapy is instituted. In this case a physiological adjustment has established itself without the aid of endocrine therapy.

The dietary habits of the hypoglycemic patient in respect to the desire for sugars and the temporary relief from eating sweets or drinking of alcohol and the onset of symptoms

one to four hours after meals keystone the structural diagnosis of hypoglycemia in the majority of cases. The symptom groups are so bizarre and mimic other previously mentioned organic disorders so closely that one cannot name any group of symptoms or single symptom as pathognomonic of the hypoglycemia. It matters not whether hypoglycemia is the only disorder or is part—and an important one—of Simmonds' disease or Addison's disease, it exists actively or potentially as an emergency or acute state to be reckoned with. This is well illustrated in the following case.

A woman, aged forty years, has had, for three years, a mild state of Addison's disease which was kept under control for eighteen recent months by the administration of 5 mg. of cortate every fifth day and increased salt intake. The patient was feeling so well that for the past few months she has discontinued routine injections of 5 mg. of cortate and has been taking the cortate only as symptoms of anorexia and "washed-out" sensations occurred.

For a period of four days this patient felt badly and remained in bed to "rest up." On the fifth day she awoke at 7 A.M. and complained of shortness of breath, dizziness and a feeling of faintness. She remained in bed and the symptoms disappeared but recurred one hour later. She arose at 8 20 A.M. for breakfast, twenty minutes later a convulsion occurred, this was succeeded by coma and she went into an extreme state of collapse with an imperceptible pulse and the blood pressure so low it could not be recorded. Ten milligrams of cortate was administered at 9 A.M. followed in ten minutes by 10 grains of caffeine-sodium benzoate and at 10 A.M. by 1 cc. of coramine. The patient remained in a critical state, the coma continued and the pulse became palpable but the blood pressure remained unrecordable. At 11 A.M. 5 grains of caffeine-sodium benzoate was administered and at 11 30 A.M. 1000 cc. of saline plus 10 per cent glucose and 1 cc. of adrenalin chloride 1:1000 was given intravenously and 5 mg. of cortate subcutaneously. The patient began to show improvement following administration of the intravenous glucose and saline and consciousness gradually returned. Ten hours after the onset of convulsions 700 cc. of saline plus 10 per cent glucose was given intravenously and this was followed one hour later by 5 mg. of cortate. The patient remained confined to bed for the following three days. Five milligrams of cortate was given twice daily and carbohydrate and salt intake was forced. During this period there was experienced a constant sensation as though there would be a return of symptoms. Improve-

ment continued and at the end of four days the cortate was reduced to a daily dose of 5 mg and eventually to a dose every third day. With this therapy the patient is now performing her normal duties.

Unfortunately no blood sugar or chloride studies could be obtained during the acute collapse of this patient, but not until the glucose and saline were administered was there any marked improvement in her condition in spite of the fact that the cardiovascular collapse appeared to dominate the clinical picture. The cardiovascular collapse appears to be secondary to the severe hypoglycemic state, since it was not found necessary to administer cardiac stimulants once the glucose and saline were administered.

This case clearly demonstrates the important aspects of blood chemistry in the acute phases of endocrine disturbances. While endocrine therapy is a requirement, we must recognize the fact that in such cases the hormone administered to correct the deficiency does not have the power to alter the blood chemistry speedily and the intravenous administration of the deficient chemical element must be utilized until the hormonal action of the administered hormone becomes effective. Cortate, which is desoxycorticosterone acetate, does not possess the positive action to raise the blood sugar, it thus differs from the adrenal cortical extract which has this quality to a better degree. The use of adrenal cortical extract is advised by Thorn in acute phases and in the crisis of Addison's disease. Thorn advises cortate later in the management of Addisonian crises.\*

When adrenal cortical extract is not available and cortate is used, adrenalin chloride, 1 cc of 1:1000 solution, is a good therapeutic agent to elevate the blood sugar and also to support vascular tone. Unfortunately its use cannot be continued but it serves a useful purpose even though its elevating effect on the blood sugar is of short duration.

In Simmonds' disease one also observes similar acute episodes due to hypoglycemia, however, the patient usually lapses directly into coma, without convulsion preceding the comatose attack. This coma is always a critical state in Simmonds' disease, since the majority of cases terminate in coma. Within the pitu-

\* Lukens, F. D. W. Disorders of the Adrenal Glands. *MED. CLIN. N. AM.*, 26:1810 (Nov.) 1942.

pituitary gland a progressive atrophy is occurring and gradually the patient enters a state in which the recoil powers within the endocrine system as a whole, with the exception of the pancreas, and the ability of the endocrine organs to support one another in opposing the action of insulin in lowering the blood sugar, is lost. The patient eventually arrives at a point where insulin is almost unopposed in its action, accordingly, in spite of all we employ by way of intravenous administration of glucose and adrenalin or the parenteral use of anterior pituitary and cortical extracts, a fatal outcome occurs. Neither of the adrenal preparations (cortical or medullary extract) can be repeatedly and indefinitely used for their blood sugar-raising properties without obtaining other major biological actions to an excessive and undesired degree.

The inability to offset therapeutically the collapse of the endocrine system in maintaining its role in elevating blood sugar has been experienced in other types of pituitary and adrenal gland disease.

One case was that of a male, aged sixty-two years, who had a pituitary cyst. The cyst was apparently a degenerative process of an eosinophilic tumor of the anterior lobe, since the patient exhibited a *formes frustes* type of acromegaly. The patient had been actively engaged as a farmer and experienced no clinical symptoms until three days prior to the acute onset of his illness and death. He first complained of headache and later dizziness and weakness but still continued to work in the fields. He suddenly lapsed into coma in the late afternoon and was admitted to the hospital in coma and cardiovascular collapse. Blood chemical studies revealed a severe hypoglycemia and low blood chlorides and sodium.

For a period of three days the patient received glucose and saline intravenously, adrenal cortical extract, adrenalin and the usual supportive treatment for cardiovascular collapse. He would regain consciousness after receiving glucose and saline intravenously but gradually the blood sugar would again fall and coma and collapse recur, whereupon intravenous glucose and saline would be readministered. This state of reaction and collapse continued until death ensued. The futility of therapy in this case was explained by the autopsy. The cyst of the pituitary comprised all but 10 per cent of the anterior lobe. The histological study of this structure showed that it consisted mainly of atrophic anterior pituitary cells. The adrenal glands were extensively atrophied and the cortex was ex-

tremely thin The histological study of the adrenal cortex also revealed atrophic and degenerative changes.

The adrenal cortex unquestionably plays a stellar role in maintaining blood sugar levels It may be either secondarily involved as in the previous case or primarily involved as in Addison's disease and the following case

The patient, a woman aged sixty-three years, had had comparatively good health prior to her present acute attack Before the breakfast hour she experienced dizziness and nausea, suddenly collapsed and lapsed into coma She also exhibited the usual signs of cardiovascular collapse The blood sugar level in this patient was so low that it could not be determined accurately and it was recorded as below 20 on three different occasions The administration of intravenous glucose did not materially alter the pretherapeutic recorded values The patient failed to respond to glucose and saline administration and supplemental therapy and death occurred forty-eight hours after the onset of her coma.

The autopsy revealed an extensive and generalized hemorrhage in both adrenal glands The cortical area was practically disrupted by the violence of the hemorrhage Again in this case the futility of corrective therapy is evident

This condition occurs more commonly in young infants than in adults and has been termed the *Waterhouse-Friderichsen syndrome* In the *Lancet*, June 26, 1943, Morison reviewed the literature of bilateral adrenal hemorrhage and reported three more cases occurring in infants In most cases this condition in infancy is associated with an infectious process and he recommends, beside hormones and supportive treatment, the administration of plasma

It should not be assumed because of such fatal cases that therapy should not be energetically and rationally pursued in cases of endocrine disease with severe hypoglycemic episodes Many endocrine patients who experience convulsions and coma due to hypoglycemic attacks recover spontaneously Such attacks occur most frequently in cases of *advanced hypogonadism* and in *eunuchoidism* In the majority of instances these patients have the convulsive seizures in the early morning hours It is known that in normal individuals the blood sugar reaches its lowest level at from 4 to 5 A.M. The attacks may also occur after fasting or excessive fatigue

Patients with hypogonadism, in fact those with any anterior

pituitary deficiency and in some instances those with hypothyroid deficiency, may exhibit what is spoken of as an insulin sensitivity or a tendency to experience hypoglycemic attacks. It can readily be seen why such patients have attacks in the early morning when the blood sugar is normally at its lowest. These attacks may occur before breakfast or with fasting for a sugar tolerance test.

Of course, nervousness and emotional upsets predispose such patients to these attacks, because of the increased utilization of carbohydrates at such periods. The management of the cases of these young hypogonadal patients is exceedingly complex. The requirements of growth and development take much of their ingested food energy and it is difficult in some instances to obtain sufficient positive carbohydrate reserves by forced feedings during the non-sleeping hours to prevent the early morning seizures. In these cases it has been found necessary to awaken the patient at midnight and give him an 8- to 12-oz. feeding of two parts milk, one part cream to which one or two level tablespoonfuls of sugar of milk is added.

These patients eventually overcome their insulin sensitivity if normal puberty and adolescence eventuates. It is my personal opinion that in young hypogonads the oral administration of anterior pituitary and thyroid stimulates gonadal development. This therapy has been fully discussed by the author previously.\* The administration of male hormone in such cases is, we believe, undesirable. Our observations show masturbation has increased the frequency of convulsive attacks in these cases after male hormone therapy. The danger of exciting penile response and a desire for masturbation outweighs the positive metabolic balance secured by the administration of male hormone.

It must be realized that young hypoglycemic patients must have their blood sugar maintained at a normal level over the twenty-four-hour period and for a period of months until gonadal normalcy is established. Consequently our endocrine therapy must be of a kind that will be effective and tolerated for a long time. There is no evidence at hand indicating that male hormone therapy with the possible exception of implant therapy will stimulate testicular development. This inability of male

\* Dunn, C. W., *Diagnosis and Treatment of Testicular Deficiency—Male Hormone Therapy* MED CLIN N AM., 26 1867 (Nov.) 1942

hormone to stimulate gonadal development we hold to be another reason against the use of male hormone in youthful hypogonadal cases. It is very evident from our studies of adult eunuchoidism that the hypogonadism is a factor in insulin sensitivity since all other anterior pituitary factors appear to be in adequate function. It cannot be definitely stated, however, that the factor of carbohydrate intake is exclusively at fault in the adolescent or adult eunuchoid with hypoglycemia.

It is known that the hypogonadal patient has a negative nitrogen balance and that the administration of male hormone creates a positive nitrogen balance and weight gain. The benefit the adult hypogonad with hypoglycemia obtains from male hormone we believe results from the carbohydrates indirectly derived from his improved protein metabolism. More important is the fact that this carbohydrate derived from protein becomes available during the latter period of absorption of the food intake and at the time he most requires it for sustaining his blood sugar until the next meal period.

The necessity for carbohydrates in the management of the thyroid crises and in the preoperative care of acute toxic hyperthyroidism is generally accepted. If the carbohydrate and chloride content of the blood is disregarded, the patient suffers or is unfortunately sacrificed during the initial management of the crises.

The subject of hypoglycemia has been discussed at some length because it does appear from our experience to be involved in the majority of acute endocrine states with the one exception of hypoparathyroidism.

#### HYPOPARATHYROIDISM

One of the occasional postoperative events in hyperthyroid patients whose toxic state requires an extensive excision of the lateral lobe is that more than one parathyroid gland is unintentionally excised and shortly thereafter parathyroid tetany develops, in a few cases a tetanic convulsion appears without forewarning. In most instances the patient presents a warning that a hypoparathyroid state is developing by complaining of cramps or stiffness in the legs, difficulty in swallowing or tightness of the facial or cervical muscles. Examination at this time will show the presence of either the Trousseau or Chvostek sign,

or both, a lowering of blood calcium, and an elevation of blood phosphorus. One cannot be certain from the level of the blood calcium as to the seriousness of the condition because some patients will experience tetanic convulsion when the blood calcium levels have reached 8.5 mg. per 100 cc. of blood, while others will not have a convulsive seizure until the blood calcium level reaches just above 6 mg. of calcium per 100 cc. of blood. In view of this it appears advisable to proceed on the basis that every patient with hypoparathyroidism must have his blood calcium brought to normal as quickly as possible.

For a period of time, even though we had available the parathyroid hormone, the treatment of hypoparathyroidism was unsatisfactory. Early management consisted in the administration in the acute phase of from 300 to 500 units of parathyroid hormone and the intravenous administration of calcium. Later, oral administration of calcium was substituted for the intravenous method and the patient was given 100 or more units of parathyroid hormone per diem. At the end of two or three months, however, the patient became insensitive to the parathyroid hormone.

To offset the failure of parathyroid hormone to act, large doses of viosterol were then given to facilitate the absorption of calcium. It is the metabolism and absorption of calcium which is defective in hypoparathyroidism, thus, merely increasing the amount of orally administered calcium is ineffective. Another therapeutic agent used was thyroid extract. Thyroid extract will mobilize calcium from its storage depots. Here it must be pointed out that in the case of the toxic thyroid of some duration the hyperthyroidism has quite naturally depleted the calcium stores and in some cases of hyperthyroidism osteoporosis occurs.

The therapeutic dilemma of chronic hypoparathyroidism appears to have been solved with the discovery of A.T. 10 marketed in this country under the name of *Hytakerol* (Winthrop). This is a 0.5 per cent solution of dihydrotachysterol in oil and 1 cc. represents 5 mg. of dihydrotachysterol. This preparation is potent in raising the level of blood calcium, in fact, its dosage must be closely checked with blood calcium studies beginning forty-eight hours after its initial administration which is exclusively by the oral method.



The dosage of A T 10 or dihydrotachysterol is from 3 to 10 cc daily for the first forty-eight hours, in the meantime clinical symptoms are controlled by the intravenous administration of calcium gluconate in doses of 5 to 10 cc of 10 per cent or 20 per cent neo-calglucon or another suitable calcium salt

Large doses of calcium gluconate or lactate, 10 to 15 gm, are administered orally As soon as the blood calcium level rises to 9.5 or 10 mg and there is an accompanying fall in the blood phosphorus, the dosage of A T 10 is reduced at least 50 per cent from its previous level A state of hyperglycemia can be quickly produced by the unnecessarily prolonged use of A.T. 10, accordingly, its dosage is regulated to keep blood calcium at from 9.5 to 10 mg per 100 cc of blood

Fortunately, many patients with hypoparathyroidism develop spontaneous cures This is believed to result from the physiological hyperplasia of the remaining parathyroid glands, as a response to the body's demand for more parathyroid hormone Thus it is desirable to encourage this physiological demand on parathyroid tissue by maintaining the dosage of A T 10 at the least required level as soon as the emergency state is passed.

The management of hypoparathyroidism therefore consists in energetic treatment during the emergency period and then gradual reduction of therapy to establish whenever possible a spontaneous cure If spontaneous cure of the hypoparathyroidism does not take place the patient must be continued on a low phosphorus diet which should be instituted as soon as practicable after the acute tetanic period has passed, and in addition, he should be given A T 10 at a dosage rate that will maintain the blood calcium between 9.5 and 10.5 mg per 100 cc of blood The treated patient must also be watched during observation for the appearance of cataract, since therapy does not prevent the occurrence of cataracts of the eye

The action of A T 10 on the blood calcium has certain sustaining qualities which permit the patient to be treated by weekly doses of from 1 to 7 cc after the maintenance level has been established Dosages in all stages of hypoparathyroidism are based on the individual requirements of the patient, and consist of that amount required for the relief of symptoms and the elevation of the blood calcium to normal range in the acute

stage, and of that amount required for maintaining the blood calcium at a normal level later. A simple, practical method for determining the approximate level of blood calcium can be utilized, namely the *Sulkowitch test*. The Sulkowitch reagent when mixed with an equal part of urine acts upon its calcium. A negative reaction indicates the absence of calcium in the urine, a low blood calcium and the necessity of increasing the dose of A.T. 10 in order to prevent or relieve symptoms. A fine white cloud in the test tube indicates a normal blood calcium level and that the dosage of hytakerol is adequate, the test should be repeated within a short time, however, in order that the cumulative action of A.T. 10 may be avoided. Excessive dosage is indicated by the formation of a milklike precipitate and under such circumstances the dosage should be immediately reduced or temporarily discontinued and the blood calcium is checked. The treated patient showing this type of test is bordering on a hypercalcemic state and may be evincing early signs of toxicity.

The symptoms of *hypercalcemia* which usually appear when the blood calcium reaches 15 to 16 mg per 100 cc. of blood are anorexia, nausea and vomiting associated with languor in the initial stages. If corrective measures such as confinement to bed, increased fluid intake, increased elimination and light diet along with regulation of therapy are not then instituted, the patient may quickly pass into a more toxic state, evidenced by headache, vertigo, abdominal cramps, thirst, polyuria, ataxia of the lower extremities and stupor. The seriousness of the above symptoms is apparent and the urgency of active elimination therapy as well as discontinuance of treatment is apparent.

In Addison's disease a similar chemical toxic state has been induced by the too liberal use of cortical extract and desoxycorticosterone acetate (cortate). In this circumstance the sodium and chloride of the blood reach abnormal levels, and as a result the body retains too much fluid and this in turn causes edema particularly of the extremities, and enlargement of the heart because of increased blood volume. This latter factor has resulted in a fatal issue, accordingly, whenever an adrenal cortical hormone preparation is used one must make sure that the blood chlorides do not rise above normal values. The treatment of

hyperchloremia consists in the release of blood volume in cases with acute cardiac signs, stoppage of therapy, increased elimination, restricted salt and light diet

#### SUICIDAL TENDENCIES IN SEVERE MIGRAINE AND HYPOGONADISM

Severe depression and melancholia leading to suicidal acts are more frequent than are commonly supposed in endocrine disorders and particularly is this true in adult hypogonadism, the climacteric and severe migraine

Every case of migraine which does not definitely respond to psychotherapy, to dietetic therapy, or the various migraine remedies, including ergotamine tartrate and histamine desensitization, should be treated with a series of large doses (10,000 to 30,000 R U) of estradiol benzoate, administered every forty-eight to seventy-two hours and even daily if the severity of symptoms fills the patient with despair and gives rise to suicidal intentions. Estradiol benzoate in a dosage lower than 10,000 R U and in some cases even 20,000 R U will aggravate the severe migraine attacks, producing violent, persistent cephalgia, intense nausea and sometimes vomiting. The physical prostration and mental reactions of the patient are similarly unfavorably affected by small doses.

Quite frequently in the more severe cases which do not respond to the previously mentioned high dosage of estradiol benzoate, as high as 80,000 R U of estradiol preparations must be administered. They are usually administered as 30,000 R U of estradiol benzoate and 2.5 mg or 5 mg of estradiol dipropionate. Since these patients are in a severe depressed state because they have not responded to the usual forms of therapy for migraine they frequently contemplate suicide, and one can never be too certain that they will not attempt it.

Lest it be felt that we are exaggerating the degree of mental disease and the suicidal tendencies in severe migraine and hypogonadism the following case history is submitted.

The patient, a male aged thirty-four years, three years ago became worried and depressed. He conceived the idea that neighbors and friends believed him to be a homosexual because he avoided all feminine contacts. To relieve his mental reactions he periodically resorted to excessive alcohol. During these periods of intoxication

he became resistive and assaultive. He had been confined to a mental hospital on two occasions, the second because he attempted to hang himself by his belt during a depressed period. Shortly thereafter he was submitted for endocrinological survey which determined the presence of a distinct gonadal deficiency, he was therefore given 25 mg of Oreton three times a week. He stated that after 150 mg of Oreton had been administered he experienced an improvement and in view of this improvement the therapy was continued and he was again paroled. Treatment was discontinued, he again became depressed, began to drink and was again mindful of the alleged homosexual insinuations. He was readmitted and shortly thereafter given an implant of 300 mg of testosterone. Under this regimen the patient returned to normal and resumed his occupation. He received an implant of 300 mg of testosterone once every three or four months.

The patient's improvement persisted until September, 1942, when he required another 300-mg implant, but owing to discontinuance of the manufacture of pellet implants it was possible to give him an implant containing only 150 mg of testosterone. He was not advised of the reduction in dosage. In three weeks he returned and complained that he had not responded. He was then given 50 mg of Oreton by hypodermic. He was quite discouraged by the results of the implant and four weeks later was given another 150-mg implant, again without advising him of the reduction in dosage. Within a short time it was necessary to administer Oreton, 50 mg hypodermically, to relieve his depressed state. He gained the conception that his condition was becoming worse because implants did not relieve him and the hypodermics of Oreton were not as effective as the implant.

In February, 1943, it became necessary to advise the patient that the dosage of the implant had been reduced and that implants were no longer available, after the one then to be administered. He received the third implant of 150 mg of testosterone on February 20. He stated that if this did not relieve him he did not know what he could do. He was requested to report on February 27, 1943. He was definitely convinced that the implant therapy had maintained him in a normal state for a period of two years while 300 mg of testosterone was being used. This was substantiated by clinical observations, behavior and employment, and records of the case. Hypodermic injections, though improving his condition, were associated with cycles of improvement and waning effect which made him unstable, as opposed to the feeling of stability and well being given by the 300-mg implant. On February 26,

1943, this patient, who during the period of observation had been cooperative and considerate and patient, placed himself in the bathtub and sent a well directed shot through his brain to end for all time the mental despair and depression which his hyposexuality produced. His lack of desire to "make a mess" and consideration of others remained with him to the end, and a useful war worker was lost because of unavailable therapy.

From this case, other reported cases and personal observations of hyposexuality, one can only be cautious of the patients' intentions once they intimate that they consider suicide, or attempt it.

#### SUMMARY

In summary, therefore, we are faced with the fact that there do exist acute episodes in endocrine disturbances. In the main they are of major proportions and in a number of instances they have a fatal outcome naturally or violently.

These patients suffer from a deficiency which is of a chemical nature. The chemicals may be inorganic and nonendocrinous, or organic and endocrinous. During the acute stage of the illness it is necessary to remedy as quickly as possible both phases of this chemical deficiency. During the period of intensive treatment and maintenance therapy it is always necessary to bear in mind that an exaggerated physiological or toxic state may be induced and this in turn may necessitate emergency treatment.

## PSYCHOSOMATIC ASPECTS OF MEDICAL PRACTICE IN WARTIME

EDWARD WEISS M.D., F.A.C.P.\*

It is generally acknowledged that about one third of the patients who consult the average physician have no definite bodily disease to account for their illness. In wartime this figure is probably somewhat increased.<sup>1</sup> In a recent study of 200 consecutive patients classified as follows: (1) those in whom the illness seemed to depend entirely on emotional problems, (2) those in whom the illness seemed in part dependent on emotional problems, and (3) those in whom an emotional problem did not seem to enter into the cause of the illness, 35 per cent were placed in the first group, 35 per cent in the second, and 30 in the last.

How should the physician deal with these patients? How should they be studied and how treated? It is the purpose of this clinic to discuss these questions briefly.

Quite commonly such patients are told that there is no evidence of organic disease, that the trouble is "functional," and they are dismissed without further attention only to land eventually in the care of some irregular practitioner or quack healer. Worse than that, the physician sometimes takes the attitude that the illness is imaginary, or that the patient is malingering, or he may assume that in some vague way the patient is deliberately responsible for the illness, refers to him as a "damn neurotic," and gives him the kind of care that must necessarily go with such a characterization. The patient may also be told that the physician does not *think* anything is the matter, but suspicion is cast upon some organ or system which needs watching and care. This happens very frequently with regard to the symptom of fatigue and the suspicion of pulmonary tuberculosis and often results in a state of chronic invalidism. Lastly, following thorough study by means of medical history, physical

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\* Professor of Clinical Medicine, Temple University Medical School

examination and laboratory investigation, some pathologic curiosity\* may be discovered which really has nothing to do with the illness. The patient is then treated as though organically diseased and is submitted to unnecessary medical or surgical treatment which, in many instances, intensifies the neurotic condition.

### EMOTIONAL PROBLEMS

What is the matter with these patients and how should they be treated? They are suffering from disturbances in their emotional lives, that is, the illness is of psychologic origin and can be satisfactorily studied and treated only from the psychologic standpoint. In civil life the ill health arises in a predisposed individual because of longstanding dissatisfaction in the business, social, or home life. The stresses of war impose further burdens upon such predisposed persons. This failure of adjustment to environment is manifested by a disturbance in some part of the personality, either as bodily symptoms of various kinds, capable of mimicking almost any disease, or as affections of the spirit resulting in attacks of anxiety, obsessions, phobias, depression, and other disturbances of mood.

Why is it that so many physicians are unwilling to admit the psychologic basis for such illnesses, or if they do grudgingly concede that "a nervous factor is present," they believe it to be of secondary importance and probably the result of physical disease? In discussing a case of this kind they are apt to say, "but there must be something the matter," meaning that there must be a physical basis for the illness and that if they are just thorough enough in their investigation, "something" will be found. However, long-time follow-up studies on such patients fail to indicate that organic disease develops in any significant number, even when it does, we must not forget that a neurotic patient may develop an organic disease that is unrelated to his neurosis just as he similarly runs a chance of getting hit by a motor car.

Every physician freely acknowledges the relation of psychic causes to such physiologic phenomena as blushing, weeping,

\* By "pathologic curiosity" is meant some congenital or acquired lesion that has no significance from the standpoint of health. Slight deviations of the nasal septum and calcified primary tuberculous lesions in the lung are examples.

goose flesh, and even on occasions to vomiting, diarrhea and so forth, but many, nevertheless, find it difficult to believe that more prolonged (chronic) disturbances of a physiologic nature can possibly be psychogenic in origin. This is due to the structural and physiologic training of modern medicine and came about in the following fashion

### THE ORGANIC TRADITION IN MEDICINE

The physician of ancient times was concerned with the spiritual basis of illness, but the structural concept introduced by Virchow led to the separation of illness from the psyche of man and a consideration of disease as only a disorder of organs and cells. With this separation of disease into many different ailments came the development of specialists to attend to all of these distinct diseases. With the specialists came the introduction of instruments of precision, and the mechanization of medicine began. Medicine now contented itself with the study of the organism as a physiologic mechanism, impressed by blood chemistry, electrocardiography, etc., but unimpressed and, indeed, often holding in contempt the investigation of the life situation of the individual, which was not considered as scientific as the results of laboratory studies. This period may in truth be referred to as the machine age in medicine. It is not to be denied that remarkable developments have occurred during this period of laboratory ascendancy, but it also must be admitted that the emotional side of illness has been almost entirely neglected.

As a consequence of this structural and physiological tradition in medicine and lack of training in psychosomatic medicine, a great many physicians pride themselves upon their unwillingness to concede the absence of physical disease when dealing with an obscure illness. This failure to recognize neurosis and treatment of the patient as organically diseased happens most frequently, as already suggested, because modern clinical medicine attempts to establish the diagnosis of a functional disorder by ruling out organic disease through medical history, physical examination, and laboratory investigation. The point that I particularly wish to make is that the diagnosis of functional illness must be established not simply by exclusion of organic disease but on its own characteristics as well. Neurosis should be a positive as well as a negative diagnosis. In other words, neurosis



has its own distinctive features to be discovered by a study of the emotional life. Only in this way can serious errors in diagnosis and treatment be avoided. If this statement is admitted, it must naturally follow that personality study is just as important in the problem of chronic illness as laboratory investigation.

#### PSYCHOSOMATIC STUDY IN CHRONIC ILLNESS

Now the question is—how do we proceed with this kind of a study? For general purposes it may be stated that in addition to the physical study it consists in simply getting to know the patient as a human being rather than only as a medical case. Too often, as already stated, the patient is looked upon only as a physiologic mechanism and is studied by means of medical history and physical examinations aided by “instruments of precision” and chemical tests. Tape measures and test tube carry the erroneous notion of exactness and thoroughness—erroneous because the emotional life of the individual, which may hold the key to the solution of the problem, is not investigated or at best inadequately so.

In regard to the latter point, too many physicians feel that they have done their duty to the study of the emotional life if they ask the patient if he is worried about anything and receive a negative reply. They are the same physicians who are apt to remark about a patient “but he doesn’t look neurotic,” perhaps believing that such a patient should by his general apprehension or by evidences of physical nervousness betray the fact that he is neurotic. Unfortunately, most neurotics do not betray any neurosis in their appearance, nor is the approach to their emotional problem so simple that the direct question—“Are you worried about anything?”—will produce information of importance. Probably the best way to deal with these patients is first to satisfy ourselves and establish their confidence by a thorough medical history, physical examination, and such laboratory tests as are necessary to exclude organic disease.<sup>2</sup> Having assured the patient that no physical disease is present, it is usually easy, by means of examples of psychic causes for such physiologic disturbances as blushing, goose flesh, palpitation and diarrhea, to make the patient understand that a disturbance in his emotional life may be responsible for the symptoms. The important clues to this disturbance can usually be found by

encouraging a discussion of problems centering around vocational, religious, marital and parent-child relationships. This is usually best accomplished indirectly rather than by direct questions. In the case of adults, domestic problems and professional and business relationships play a large part in functional illness. In young unmarried people, family relationships, the choice of a career, and often religious and sexual problems are important for discussion. War problems, of course, concern both.

#### THE CIVIL APPLICATION OF MILITARY EXPERIENCE

In these days when there are so few physicians left to carry on civil practice it is, of course, necessary for them to do their work in the shortest possible time. Obviously this will not permit a lengthy interview for many patients but a way must be found to provide time for the few who really need it. Experience gained in induction board work provides a clue in this regard because there an immense number of men have to be examined in a very short time. Hence the neuropsychiatrists have worked out a system to screen out the maladjusted. One such technic, as employed at the Boston Induction Station,<sup>8</sup> is employed during the neurological part of the examination and afterwards, when questions are asked in about the following words: "How is your general health? Have you ever been seriously sick? Any bad accidents? Have you ever been knocked out? Do you ever have headaches? Dizzy spells? Fits or convulsions of any kind? Any stomach trouble? Nervous trouble? Have you ever had a nervous breakdown? Has anyone in your family ever had one? Or any of the other things I've just asked you about? How old are you? What work do you do? What before that? What's the longest job you've held? How far did you go in school? How much do you drink? Have you ever been arrested? What do you think about going into the Army?" Or with a volunteer, "Why are you joining the Army?"

Of course, depending on the answers, other questions are asked—for example, "How old when you quit school? How many grades did you have to repeat?" or, "How much time have you lost from work in the past year on account of sickness?" And where mental deficiency is suspected on the basis of school and individual history, and, still more, on the basis of response to questions, directions and general attitude, "How

much is a half of a half? What year is this? Why it is called that? Why does the sun rise in the morning and set in the night?" Those men at marginal level are referred to the psychometrist for examination. His report is added to the work-sheet and the man comes back to the referring psychiatrist who makes the final decision as to acceptance or rejection.

The authors go on to say "As has been noted, examinations have been carried out by many different examiners. Two facts emerged very quickly. First, a neuropsychiatrist of clinical experience, thrust into this situation, presented with the problem and the general knowledge roughly of the criteria of acceptance, quickly worked out a technic of examination which satisfied him. It is extremely interesting that the technic evolved by so many different men was so nearly similar—a fact suggesting that the solution to the problem was probably fairly correct, since it was independently arrived at by many different examiners. It is of further interest that numerous published reports from centers all over the country describe remarkably similar technics of examination. The second point was the remarkable uniformity of rejection rate of the examiners with the greatest clinical experience. This figure ranges from 6 per cent to 9 per cent. Some examiners averaged as low as 1 per cent, some as high as 16 per cent. When one considers the clinical background of the various examiners, it seems reasonable to assume that the true incidence of rejectable defects discoverable in such an examination as this is somewhere in the neighborhood of 7½ per cent, and that those examiners whose rejection rate was consistently much lower were failing to find pathology, or had too lenient a standard."

#### BODY LANGUAGE

I often tell my patients that if they cannot find an outlet for tension of emotional origin by word or action, the body will find a means of expressing this tension through a kind of "body language." For example, if a patient cannot swallow satisfactorily and no organic cause can be found, it may mean that there is something in the life situation of the patient that he "cannot swallow." Nausea in the absence of organic disease sometimes means that the patient "cannot stomach" this or that environmental factor. Frequently a feeling of chest oppression accompanied by sighing respirations, again in the absence of

organic findings, indicates that the patient has a "load on his chest" that he would like to get rid of by talking about his problems. This kind of an explanation applies to a great variety of symptoms and often appeals to the patient as a common-sense approach to the emotional factor in illness. Again and again it has permitted me to understand something about the life situation of the patient.

### SEXUAL FACTORS

This is too large a subject to cover in a short paper, but one point of special importance does deserve consideration and that is the relation of sexuality to neurosis. Ever since the introduction of the epoch-making studies of Freud to the problems of neurosis, medicine has misunderstood his conception of sexuality. He has often been quoted to the effect that disturbances in genital activity are the sole cause of the neuroses. This is quite far from the truth. It is rather that difficulty in the sexual sphere appears as a revealing index to a neurotic personality and can be looked upon in that light. In other words, in much the same manner that urea retention serves as an index to an impending uremia so do disturbances in the sexual life of the individual, such as varying degrees of frigidity in the female and varying degrees of impotence in the male, serve as a reliable index to the kind of a personality that is very liable to develop a neurosis.

### APPLICATION OF FINDINGS

Many physicians will ask "Well, suppose you do find something of importance in the emotional life of the patient, some conflict that is causing illness, what can you do about it? What good does it do the patient to know?" First of all, it is often a great help to the patient to know that the ailment is not organic in origin but is due to a disturbance in his emotional life. It gives him a great deal of reassurance and is the first step in the right direction. When a symptom is divorced from the fear of organic disease, cancer, for example, it becomes easier for the patient to tolerate the symptom and, surprisingly enough it may, and often does, disappear. Secondly, such knowledge and such an approach will frequently save the patient unnecessary, troublesome and expensive medical or surgical treatment with a resulting further degree of invalidism.

Often just the talking out of the problem with the physician will alleviate symptoms, and frequently some simple adjustment will accomplish real help. This caution must be sounded, however, it is a good rule for the physician to listen rather than talk, giving advice on important emotional matters is dangerous. For just as there is major and minor surgery, so there exist major and minor forms of psychotherapy, and while the average physician should not attempt major forms of psychotherapy, he must be able to recognize the severe neuroses so that he may refer them elsewhere for treatment. He should be able to deal with the simpler neuroses not only for the purpose of helping such patients in a positive way but also to save them from unnecessary medical and surgical treatment and exploitation by quacks and irregular practitioners.

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## EPIDEMIC KERATOCONJUNCTIVITIS\*

ALSON E. BRALEY M D †

IN 1941 a severe form of acute conjunctivitis appeared in the shipbuilding plants of San Francisco. It spread quickly through several industrial plants and to the civilian population. This epidemic disease received considerable publicity and came to be known as "shipyard conjunctivitis" or "California conjunctivitis." Since its inception in California the disease spread quickly to the East coast and thence toward the South and Midwest. Because the names "California conjunctivitis" and "shipyard conjunctivitis" were not considered descriptive, the name "epidemic keratoconjunctivitis" was suggested and quickly adopted. Apparently the disease was present in California before it reached epidemic proportions in San Francisco because Hobson<sup>1</sup> in 1938 reported sixteen cases of a superficial punctate keratitis from a veterans' hospital in San Fernando, California. From his reports it appears that most of these might have been similar to those later reported by Rieke,<sup>2</sup> de Roeth,<sup>3</sup> and Hogan and Crawford<sup>4</sup> as epidemic keratoconjunctivitis.

Similar diseases have been reported under several different names. In 1889 Fuchs<sup>5</sup> observed in an epidemic thirty-eight cases of a disease he called "superficial punctate keratitis." The keratitis was preceded by an acute conjunctivitis. A close similarity is noted between the disease he described and the present disease. In his description, he stated that it was a form of superficial keratitis related to herpes febrilis corneae but not associated with the formation of vesicles. These corneal changes had a predilection for the superficial layers and were concentrated in the central portions of the cornea. He also emphasized

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\*From the Department of Ophthalmology, College of Physicians and Surgeons, Columbia University, and the Institute of Ophthalmology of Presbyterian Hospital, New York City.

† Assistant Professor, Department of Ophthalmology, College of Physicians and Surgeons, Columbia University, and Assistant Attending Surgeon, Vanderbilt Clinic and Presbyterian Hospital, New York City.

that the disease was frequently unilateral and that following the recovery from the acute conjunctivitis, pain, photophobia and lacrimation were common. Reports by Adler,<sup>6</sup> Von Reuss<sup>7</sup> and others indicate that there must have been an epidemic of the disease in Vienna in 1889.

A similar disease was reported in 1900 by Herbert<sup>8</sup> who observed twenty-six cases in Bombay. The disease must have become endemic since no further reports of the disease appeared until 1920 when Kirkpatrick<sup>9</sup> made a short report of a similar disease. Then Wright<sup>10</sup> and later Kirwin<sup>11</sup> described extensive epidemics in Madras, India. It would seem from these reports that the disease must have been fairly widespread in India between 1920 and 1933. Outbreaks of a similar disease occurred in India and China from 1933 to 1936, in Germany again from 1938 to 1940 and in Malaya from 1935 to 1938. Hamilton<sup>12</sup> in discussing a survey of eye diseases in Tasmania, described numerous cases similar to our present disease. Holmes<sup>13</sup> in 1941 reported 10,000 cases in Oahu, Hawaii. From these findings, it would seem that the disease was epidemic in the Near East and East Indian islands. Some of the cases reported, however, are not identical with the disease as I have seen it but certainly there were a large number of cases in that area before the disease appeared on our West coast. It seems possible that the present epidemic may have begun in Malaya, spread to Hawaii and then to our West coast.

It is difficult to determine just how many cases have occurred in the United States since 1941. Whenever an epidemic occurs, it is always possible that a large number of cases of other types of conjunctivitis may be mistaken for the epidemic disease. I have observed over 2000 cases from the New York area. If this area represents approximately 10 per cent of the total population of the United States, then there may well have been 20,000 cases in the entire population.

#### THE CLINICAL DISEASE

In order to present a clinical picture of the disease the following case is cited:

Mr. R. H. had been followed in the Vanderbilt Clinic for five years because of a chronic glaucoma. He was a night clerk in a small New York hotel and came in contact with many people. His

conjunctiva and cornea had always been normal and the tension was controlled with 2 per cent pilocarpine

In June of 1942, Mr R H appeared at the Vanderbilt Clinic with a history that the previous night he had felt a sudden sharp pain in his right eye. This was associated with a marked foreign body sensation. He was unable to find a foreign body but the sensation and occasional sharp pains continued. By the following morning he had considerable edema of the upper lid and it was difficult for him to open his eye. The foreign body sensation still persisted and there was moderate pain and discomfort in the eye, especially on movement of the eyeball. Vision in the eye was normal. There was considerable edema of the right upper lid and moderate chemosis was present. The conjunctiva was smooth, the blood vessels distended. There was edema of the semilunar fold and caruncle but little edema of the lower lid. A preauricular lymph node was not palpable. Cultures from the conjunctiva grew diphtheroids and a few colonies of *Staphylococcus aureus*. Scrapings from the conjunctiva showed epithelial cells with numerous mononuclear leukocytes, no polymorphonuclear leukocytes were found.

By the second day the edema had increased somewhat. The conjunctiva showed numerous follicles on the lower lid and a few follicles on the lateral margins of the tarsus of the upper lid. The edema of the caruncle and semilunar fold was more marked and there was a painful, slightly tender preauricular lymph node. He stated that he had a slight head cold and some headache. His temperature was 98.6° F. He complained of an occasional foreign body sensation in the left eye.

During the next five days the clinical findings gradually increased until he was unable to keep his right eye open. Photophobia was not marked. On the fifth day the edema was decreasing and the preauricular lymph node was smaller and less tender. However, submental and submaxillary lymph nodes were present. On the sixth day the patient noted moderate photophobia for the first time. A few fine subepithelial opacities were seen in the cornea with the slit lamp. The cornea did not stain with fluorescein. The edema of the left eye had increased but was not as severe as it had been in the right eye. There was also a preauricular lymph node on the left side.

On the eighth day the conjunctivitis in the right eye had improved but the photophobia was more marked and numerous half-millimeter whitish opacities could be seen in the cornea. These opacities were just beneath the epithelium and although the epithelium seemed slightly raised over some, they did not stain with fluorescein. Approximately thirty opacities were counted in the



central portion of the cornea and all of them seemed to be localized in or slightly superficial to Bowman's membrane. The opacities were circular and composed of numerous fine dots, when viewed with the high power of the slit lamp. The preauricular lymph node was just palpable. Vision in this eye had decreased to 20/70. Although the acute conjunctivitis in the left eye was decreasing, a few corneal opacities were also present.

The acute conjunctivitis lasted four weeks in each eye, seeming to improve rather slowly during the last week but the visual disturbance and corneal changes persisted. Photophobia was still present, especially marked in artificial light. Six months later the vision in the right eye had improved to 20/30 and numerous subepithelial corneal opacities were present. In the left eye there were a few corneal opacities and the vision was not disturbed. These corneal opacities seemed to have become thinner. They were circular and composed of numerous fine dots but the number of dots present in the individual opacities seemed to decrease gradually. One year later, the right cornea showed eight opacities while the left eye had two. No scars were present from previous opacities. The vision in the right eye was 20/30 and photophobia in artificial light was mild.

From this case and many concurrent cases a light of clinical findings present themselves. The most common early symptoms are *foreign body sensation* associated with pain and lacrimation. The *edema* of the upper lid, bulbar conjunctiva, caruncle and semilunar fold are striking. This is associated with or followed by a *follicular conjunctivitis* accompanied by preauricular lymphadenopathy. *Tearing* is marked but purulent discharge is rare. The lids feel sticky and scratchy but are not stuck shut as is so frequent in acute bacterial conjunctivitis.

Frequently *small hemorrhages* are seen on both the bulbar and palpebral conjunctiva but these are not as severe as frequently seen in acute pneumococcal conjunctivitis. The more severe cases many times develop a *pseudomembrane* on the lower palpebral conjunctival surface. This pseudomembrane is thin when compared to the thick pseudomembrane of a streptococcal conjunctivitis, but much thicker than the very fine pseudomembrane associated with allergic conjunctivitis. A membrane may also be present on the upper lid. A pseudomembrane was present on the third to fifth day in 67 per cent of the cases. The pseudomembrane when examined microscopically was composed almost entirely of epithelial cells with mononuclear cells scat-

tered throughout. When the pseudomembrane is light yellow in color it contains many more mononuclear cells and degenerating epithelial cells. This was usually present on the fifth to the seventh day. Early the slightly opaque translucent membrane is composed almost entirely of viable superficial conjunctival cells. I was unable to demonstrate virus bodies (inclusion bodies) in any appreciable number although when the membrane is stained by the Giemsa method an occasional blue staining body could be seen in the cytoplasm. Victoria blue stain failed to demonstrate any virus.

The typical *subcorneal infiltrations* usually develop on the eighth or ninth day of the disease but they may develop as early as the fourth day or as late as the twenty-first day.

#### EARLY DIAGNOSIS

The diagnosis of epidemic keratoconjunctivitis during the early stages before the development of the typical corneal opacities, is difficult. A common styne near the outer angle of the upper lid will give rise to considerable edema with a large preauricular lymph node and occasionally a few follicles on the conjunctiva. The styne of course becomes apparent in a few days. Nearly any of the acute bacterial types of conjunctivitis may be associated with edema, a preauricular lymph node and to a lesser extent, follicles. However, in nearly all acute bacterial conjunctivitis, the polymorphonuclear leukocytes are predominant in the conjunctival secretion.

The early diagnosis of epidemic conjunctivitis then is dependent upon acute symptoms with or without preauricular lymphadenopathy and the finding of large numbers of mononuclear leukocytes in the conjunctival secretion. Here again, however, one disease which also has a tendency to run in epidemic form, called "Beal's conjunctivitis," shows only mononuclears in secretion smears. The early diagnosis is then based on clinical impressions and laboratory findings before the corneal infiltrates develop. It is not possible to use the preauricular lymph node as a criterion in differential diagnosis, since it may be enlarged in other diseases as well. I have seen a number of typical cases of epidemic keratoconjunctivitis that did not show a palpable preauricular lymph node when examined. Some of the cases observed from the onset of the disease showed only

a transient preauricular lymphadenopathy The lymph node was palpable during the first or second day of the disease and disappearing thereafter In some cases, however, the lymphadenopathy persisted for months after the acute conjunctival symptoms had subsided

#### ETIOLOGY

A good deal of material for experimental use was obtained from Mr R H This material was given to Dr Murray Sanders who succeeded in isolating a filtrable virus Doctor Sanders placed the scrapings from the conjunctiva into fluid tissue cultures, which were allowed to stand at room temperature The infected tissue cultures were ground and inoculated intracerebrally, intraperitoneally and intravenously into young 10- to 12-gm white mice The mice developed encephalitis in from three to five days, which when passed to other mice or back to tissue culture, finally became a potent virus Blood serum from the patient neutralized the virus obtained by Doctor Sanders He was able to isolate a similar virus from other sources and found that patients recovering from epidemic conjunctivitis had serum antibodies\* to his virus If Doctor Sanders'<sup>14</sup> work is confirmed by other investigators, then there is little doubt that the disease is due to a filtrable virus The fact that patients recovering from the disease carry immune bodies in their serum may indicate that they are probably immune to further attacks of the disease

#### EPIDEMIOLOGY

The epidemiology of an outbreak of epidemic keratoconjunctivitis from the Schenectady, New York, area was reported by Perkins, Korns and Westphal<sup>15</sup> Their reports are of a great deal of interest The acute conjunctivitis in their series was bilateral in 56 per cent of the cases, corneal opacities developed in 85.5 per cent of which 28.4 per cent were bilateral The corneal opacities occurred from the seventh to the twenty-third day in 92 per cent of the cases and the clearing-up of the opacities was slow In their series they noted that the highest incidence of infection occurred in the dispensary These authors were unable to demonstrate any definite relationship between the dispensary and the individual cases of epidemic keratocon-

\* The word "antibodies" is used advisedly for want of a better term I mean the substance in the plasma which neutralizes the virus

junctivitis but it seemed to be suggested that the dispensary was the important place of the transmission of the disease. In a study conducted recently by Sanders, Gulliver, Forcheimer and Alexander<sup>10</sup> it was suggested from the charts that individuals obtained their infections in a physician's office.

From my own experience a number of individuals have contracted epidemic keratoconjunctivitis in periods from five to fourteen days after being exposed to a case in the clinic. Two patients are of interest.

An attending ophthalmologist at Vanderbilt Clinic was demonstrating cases of conjunctivitis to a group of medical students. One case was an early epidemic keratoconjunctivitis, the diagnosis of which was somewhat obscure. Five days after demonstrating this case, he noted a foreign body sensation in his left eye with considerable discomfort, especially on rotation of the globe. The symptoms gradually became worse until there was considerable chemosis and edema of the upper lid. He followed the usual course of the disease with the disease becoming bilateral on the third day after the first eye had become involved. Corneal opacities developed in the left eye on the eighth day and a few in the other eye on the twelfth day.

The original patient demonstrated, had a more virulent infection as judged by the amount of edema and conjunctival reaction but the number of corneal opacities in both were approximately the same. The husband of the patient demonstrated by the physician also developed epidemic keratoconjunctivitis.

One case has been called to my attention in which the tonometer used for measuring intraocular pressure may have transmitted the disease to a second patient. Although the clinics and dispensaries are being incriminated as the source of transmission, a great many patients have been seen who had not had any previous contact with either a physician's office or a clinic. There may be a mild upper respiratory infection associated with the disease. In crowded places it is not unlikely that droplet eye infections may occur. With this thought in mind, two other patients are of interest.

Miss N was an operating room nurse in a large local hospital. She came in contact with very few people. On her day off she went on a shopping tour and visited several large department stores.

To her knowledge, she did not encounter anyone with acute conjunctivitis. One week after her tour she developed acute conjunctivitis in her left eye which became a typical epidemic keratoconjunctivitis.

Miss C P was a director of occupational therapy in a large hospital for chronic diseases and her directing duties were such that she rarely came in contact with anyone except the personnel of her department. She made a train trip and likewise did not knowingly come in contact with any cases of acute conjunctivitis but eight days later developed an acute case of what subsequently proved to be epidemic keratoconjunctivitis.

These cases illustrate the possibility of infection either by fomites or droplets from individuals who may or may not have the disease. Both of these infections occurred during the time the disease was quite widespread in the city.

It would appear from these findings that the disease is quite contagious. However, during the study of the epidemic in the Schenectady area, approximately six physicians examined the patients without contracting the disease. The only care observed was that of washing one's hands after each examination.

The only possible conclusion to be drawn from the epidemiological studies is that the disease may be transmitted from one individual to another either by direct transmission or by a third party. I was told by one physician that he probably transmitted the disease to two of his patients before he was aware that he had the disease. The studies of Sanders, Gulliver and associates<sup>16</sup> seem to indicate that the ophthalmologist may have transmitted the infection in the cases they studied. The second possibility of fomite or droplet infection from individuals without the disease is much more remote.

The possibility of *corneal foreign bodies* contributing to the transmission of the disease has been considered. In a number of cases seen at the Vanderbilt Clinic, a few gave the history of a corneal foreign body. From the records of the clinic three cases have been chosen whose histories are so similar that a summary of one will be sufficient.

Mr P was a hospital employee who got something in his left eye on his way to work. He reported to the Vanderbilt Clinic and under pontocaine anesthesia a small foreign body was removed.

from his cornea without much difficulty Sulfathiazole was placed in the eye and the eye covered The following morning the corneal abrasion had healed and the eye looked normal Six days later, he again returned with an acute conjunctivitis and a tentative diagnosis of epidemic keratoconjunctivitis was made This was subsequently confirmed when the typical corneal changes occurred

There is little doubt in my mind that he was inoculated with epidemic keratoconjunctivitis when the corneal foreign body was removed. There is a possibility that the foreign particle may have carried the infection into the eye However, during the period of the epidemic, comparatively few cases with corneal foreign bodies developed the disease

#### RESULTS OF THERAPY

At the present writing, 229 cases have had controlled treatment Of this number, the majority were treated with either 5 per cent sulfathiazole ointment or 0.25 per cent pontocaine and 1:2000 adrenalin The patients received considerable symptomatic relief from the use of a local anesthetic and a vasoconstrictor The 5 per cent sulfathiazole ointment seemed to make most of them more uncomfortable and did not shorten the course of the disease Local 2 per cent penicillin was used in three cases without beneficial effect Ten cases were treated with sulfathiazole sesquihydrate without any appreciable effect To date five cases have been treated with 20 mg per cent tyrothricin, which, when freshly made, seems to decrease the severity of the acute conjunctivitis but does not prevent the formation of the corneal opacities.

Since individuals recovering from epidemic keratoconjunctivitis develop immune bodies to the virus, *convalescent serum* and later *plasma* were obtained and given to patients with early epidemic keratoconjunctivitis The antibody titer of the convalescents was checked at intervals and when this titer was highest, blood was withdrawn and processed by Dr John Scudder and his group Fifty cubic centimeters of convalescent plasma were then injected intravenously into patients suffering from epidemic keratoconjunctivitis on the second to fourteenth day of the disease In the first group of ten patients there was one failure<sup>17</sup> In the next ten, three failures were encountered Of the three failures, two individuals had already developed

corneal opacities while the other received the plasma on the seventh day of the disease and developed opacities on the following day. The primary criteria used in evaluating the treatment was the development of the corneal opacities. Since a positive diagnosis could not be made without the typical corneal opacities, all treated patients were checked periodically to determine the antibody titer of their serum. All individuals, whether considered as successes or failures, developed antibodies. Since it is possible that the convalescent serum may stimulate the formation of antibodies, five patients with purulent conjunctivitis were given convalescent plasma and none of these patients developed antibodies to the virus isolated by Doctor Sanders.

From the results of therapy it will be seen that the only substance in my hands that has been successful in preventing the development of corneal opacities has been convalescent plasma. From this small series of twenty cases, it would appear that the convalescent plasma must be given early, preferably before the third day and not later than the fifth day of the disease. The majority of the patients experienced a sense of complete symptomatic relief during the first forty-eight hours after receiving convalescent plasma.

#### SUMMARY

- 1 Diseases similar to epidemic keratoconjunctivitis have been reported at intervals since 1889.

- 2 It is probable that our present epidemic began in Malaya in 1938 from whence it spread to Hawaii and the continental United States.

- 3 The clinical features of the disease consist of edema, lymphoid hyperplasia, enlarged preauricular lymph node, marked tearing with no purulent discharge and the typical subepithelial infiltrations.

- 4 The cause is probably a filtrable virus.

- 5 Patients recovering from the disease have immune bodies to the virus in their serum.

- 6 Epidemiology is obscure but certainly in a few epidemics the physician was responsible for the transmission of the disease. Simple hygienic measures, chiefly cleanliness of the hands, seem to prevent transmission.

- 7 Convalescent plasma seems to be the treatment of choice.

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# A THERAPEUTIC EVALUATION OF BENZEDRINE SULFATE IN THE TREATMENT OF SEASICKNESS RESULTS IN 100 CASES

FREDERICK K. ALBRECHT, M.D.\*  
United States Public Health Service

SEASICKNESS has been widely discussed and with diversity of opinion as to its cause, but no treatment has as yet been perfected on a rational basis. The rolling and pitching of ships causes unusual stimulation of the semicircular canals as a result of the continuous movement of endolymph and irritation of the receptors. Predisposing causes are poor ventilation, unpleasant odors of a ship's hold, constipation, migraine, disturbances of orientation, vagotonia, gastro-intestinal disturbances, and psychic impressions as seen in those who become seasick before the vessel sails, or from seeing and hearing the distress of others who are ill.

Abnormal conditions induced by unusual movements are not limited to man. Seasickness has been noted in horses, dogs, cattle and sheep. It is stated that women and neurotics are unusually susceptible to seasickness. Racial differences have been described in the literature, and in my own experience Filipinos and Puerto Ricans were noted to be very susceptible. Deaf-mutes and those in whom the vestibular apparatus is destroyed are free from vertigo by virtue of labyrinthine aplasia. Children accustomed to spinning, infants, and the aged are relatively immune to seasickness.

The most seasoned passenger or crew member may develop seasickness. Lord Nelson, the hero of many British naval battles is said to have been seasick most of the time. Different vessels have their peculiarities of roll and pitch and a seasoned sailor on one ship may become violently ill on another ship, or a passenger during his first sea voyage may escape seasickness only to be stricken on a subsequent voyage. Some sailors acquire their "sea legs" soon while others, like the writer, never acquire them.

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\* Passed Assistant Surgeon, U. S. Marine Hospital, Baltimore, Maryland

## SYMPTOMS AND SIGNS

The basic symptoms are anorexia to food, salivation, cold sweats, pallor, vertigo, headache, nausea, vomiting and retching. Intestinal spasm may cause severe cramps, and diarrhea, palpitation and collapse may also be a part of the clinical picture.

Hill of the Aquitania has classified the symptoms as referable to the sympathetic and parasympathetic nervous systems

Symptoms	<i>Vagotonia</i> (More common in men)	<i>Sympatheticotonia</i> (More common in women)
Nausea	Variable	Constant
Vomiting	Absent or only at long intervals	Frequently repeated
Relief of nausea following emesis	Usually marked	Slight or transient
Headache	Early, persistent, often occipital or vertical	Late if present and usually frontal
Vertigo	Early	Late
Pulse rate	60 or less	80 or higher
Blood pressure	Low	High

Hill attempted to separate the symptoms for the purpose of treatment, but there is usually a crossing of the characteristics in the same case and no two cases are exactly similar. I became acutely aware of this subject while acting as Medical Officer aboard a Coast Guard cutter in the Caribbean Area during 1941-42. The 100 cases reported upon here represent for the most part U S Coastguardsmen stationed at Puerto Rico, St. Thomas, Virgin Islands, Miami, Florida, and Key West, Florida.

For some reason seamen greatly dislike to admit being seasick, and when forced to come to the sick bay, they will deny seasickness but will complain of other ailments ranging from low back pain to headache in the hope that they will be put on the sick list and be allowed to stay in their bunks. Just why being seasick should be considered a disgrace is not entirely clear when we realize that some folks have been going to sea all their lives and have never been able to be entirely free of this malady. Instead of "kidding" these patients and thereby destroying the rapport between doctor and patient, I have found that by confessing my own inadequacy at sea, the most hardened seaman after some hesitation will readily admit that seasickness is also his chief difficulty. These persons suffer much at times from abuse heaped upon them by fellow crew members. It is un-

fortunate that not too many officers can be found aboard ships whose sympathy and understanding encompasses such "trivial" matters as seasickness. Some of these patients develop a psychoneurosis, others attempt or contemplate "jumping ship," and I recall a few cases of attempted suicide due to a feeling of inadequacy aggravated by the torments of fellow crew members.

#### RESULTS IN 100 CASES OF SEASICKNESS TREATED WITH BENZEDRINE SULFATE

This study presents the results achieved on 100 patients, seventeen of whom were women of whom the majority were from service families returning to the mainland of the United States. Most of them were well traveled and had been to sea many times. The balance of the group consisted mainly of Coast guardsmen, as previously mentioned.

#### CLINICAL PICTURE IN 100 CASES OF SEASICKNESS

##### *Age of Patients*

Varied from 17 to 42 years

##### *Duration of Symptoms*

20 years	1 per cent
7 years	1 " "
5 years	4 " "
3 years	8 " "
1 year	20 " "
6 months to 1 year	28 " "
Less than 6 months	38 " "

##### *Symptoms*

Nausea	91 per cent
Vomiting	80 " "
Headache	86 " "
Occipital	10 per cent
Vertical	50 " "
Frontal	12 " "
Generalized	14 " "
Salivation	34 " "
Sweating	36 " "
Prostration	13 " "
Anorexia	80 " "
Refused all food	29 per cent
Only liquids tolerated	16 " "
Food tolerated only in recumbent position	3 " "
Mild, variable, only in rough water	32 " "
Vertigo	50 " "

*Other Features*

Previous neurotic history (2 cases were failures)	4 per cent
Previous history of gastro intestinal disorders (6 were failures, 4 of whom were chronic alcoholics)	10 " "
Previous air or car sickness (3 failures)	14 " "

FOLLOWING ADMINISTRATION OF THE DRUG

*Symptoms*

Xerostomia	11 per cent
Insomnia	2 " "
Euphoria	8 " "
Rash	2 " "
	(Questionable)
Habituation	0 " "
Palpitation	0 " "
Irritability	1 " "

*Failures*

Complete (Men, 15 per cent women, 3 per cent)	18 per cent
Equivocal (Men 1 per cent women, 3 per cent)	4 " "

*Complete Relief of Symptoms* 78 per cent

*Comment*

The dosage of the drug varied from 15 to 30 mg daily, and in all cases it was given in divided doses. It was found that in many cases where the patient had arisen from the recumbent position, once he assumed the erect position and the swaying motion of the vessel had caused the chain of symptoms to begin, emesis would prevent the ingestion of the drug. Accordingly, in almost all cases where practicable, the drug was advised to be taken from five to ten minutes before the patient arose from his or her bunk. All cases were carefully controlled using placebos which had the same form and taste as the original benzedrine sulfate tablet. In the overwhelming majority of cases, when the drug was replaced with the placebo most of the symptoms returned, and when the drug was again given the patient all troublesome symptoms disappeared and the patients were able to resume activity, enjoy walking about the deck and eating without any difficulty. Some of the U S Coastguardsmen patients had been going to sea for from five to twenty years and had never known complete relief before in rough water until

taking benzedrine. In some the symptoms were not severe enough to cause them to lay off duty but they were unable to eat and were not able to do efficient work. As a result they were frequent callers at the sick bay and some were even sent to hospitals for the treatment of migraine and gastro-enteritis.

*Complete Relief of Symptoms*—In 26 per cent of the total group, complete amelioration of symptoms was secured by the administration of 10 mg. of the drug before arising and 5 mg. twice daily. A striking improvement was noted in these patients. The Coastguardsmen were able to eat, stand their watches in all sorts of weather and their morale improved greatly with their increased tolerance to the pitching and rolling of the vessel. Stewards who formerly became sick at the sight and smell of food during rough weather were able to carry on their duties without difficulty. Firemen and oilers who were made ill by both the motion of the vessel and the smell of Diesel oil were able to work without further nausea, vomiting, or anorexia.

Another group of twenty-five patients (25 per cent) noted symptoms only in very rough weather. They were unable to carry on their duties but received some relief from assuming the recumbent position. Complete relief of all symptoms followed the use of benzedrine and they were able to carry on their duties in all weather.

The remainder (27 per cent) of the patients securing complete relief from benzedrine were those who became violently ill in mild weather or from even a slight rolling motion of the ship. While all received complete relief from the drug, an immediate return of the symptoms was noted upon the administration of placebos.

Two patients were in the third, one in the fourth, and one in the sixth month of pregnancy. All were violently ill and received complete relief of symptoms from 10 mg. of benzedrine three times daily.

*Failures*—Of the failures (22 per cent), six gave a previous gastro-intestinal history of gastric upsets and of these six, four were chronic alcoholics. Six other failures were considered neurotic either by a previous history or by observation. Three other failures gave a history of previous car or airsickness.

*Blood Pressure*—It was possible to check the blood pressures in only 71 per cent of these cases. In no case was there an appreciable rise in either the systolic or the diastolic pressure.

In 6 per cent there was a drop of from 5 to 7 mm of mercury in the systolic pressure

*Loss of Weight*—Thirty-four per cent of the patients reported a loss of weight, in some cases ranging from 8 to 20 pounds, before taking benzedrine. In *all* cases, the patients were able to resume eating and gained back all the weight lost. Before taking benzedrine, the writer lost 14 pounds per week while at sea in rough weather. Atropine and several antispasmodics and sedatives were tried to no avail, but following the administration of benzedrine sulfate, 20 mg daily, he regained his normal weight.

*Habituation*—In no case was there any sign of habituation, nor was there any increased tolerance to the drug noted. In fact, in many cases it was possible to decrease the dosage of the drug, but it is noteworthy that where this was possible and placebos were given, all or many of the symptoms returned promptly.

*Other Features*—Xerostomia was present in 11 per cent of the cases but in no case was it troublesome, it was relieved by chewing gum. The two cases of rash which occurred were questionable in that both patients had eaten sea food for which there was a definite allergic history. Euphoria was noted particularly in those cases in which the patient drank much strong black coffee (aptly called "boiler compound" by seamen) in order to keep awake on long watches. While anxiety was present in some of the failures, since it had been present before the drug was given we did not consider the drug as a factor in its etiology.

#### SUMMARY

One hundred cases of seasickness are described with symptoms before and after receiving benzedrine sulfate. All cases were carefully controlled. This study, limited as it is, suggests that benzedrine given in proper dosage and under the supervision of a doctor (not entirely necessary) is a safe drug for the prophylaxis of seasickness. Its use permits the patient to be up and about and to partake of his usual nourishment. There are no distressing drug symptoms and no evidences of habituation. This drug might well be used by our armed forces to good advantage. None will deny that a seasick soldier or sailor is of little help to himself or to others, in fact, he is a distinct liability as he requires attention from other personnel who might

be better employed at the time In the case of members of the armed forces unaccustomed to sea travel who are enroute to the theater of operations or are engaged in landing operations, the drug would not only prevent a great percentage of seasickness in those susceptible, but it would also provide a possible beneficial psychomotor stimulus as well

## BILIARY DRAINAGE BY DUODENAL INTUBATION\*

WILLIAM DALE BEAMER M.D.†

PAST and present experience with upper intestinal intubation renders it desirable to reevaluate our ability to make adequate examinations of the biliary tract by collection of bile from the duodenum. Certainly the procedure as commonly practiced by those not thoroughly indoctrinated in the use of the duodenal tube often leads to inconclusive results, when but little basic knowledge is necessary for correct interpretation of the findings. It is my purpose here to review the principles and to recognize those factors which produce unsatisfactory results.

### HISTORY OF DUODENAL INTUBATION

The use of a mechanical device to empty the gastro-intestinal tract was initiated by Kussmaul, who first practiced gastric lavage in 1867.<sup>1</sup> The first serious attempt to enter the duodenum came twenty-eight years later when Hemmeter<sup>2</sup> used a combination of two tubes. On the distal end of one tube was a balloon grooved on its upper surface when inflated in the stomach. The groove was designed to act as a guide for the entrance of the second tube into the pyloric canal. Obviously such an arrangement, although ingenious, could not be practical because of the difficulty and often impossibility of placing the distal end of the groove opposite the pylorus. Kuhn<sup>3</sup> in 1898 attempted to improve upon this by inserting a wire spiral in an ordinary stomach tube, and by patient and painstaking manipulation to insert it into the duodenum. Thus matters stood until 1909 when Linhorn<sup>4</sup> developed a small bore, soft rubber tube which ended in a perforated metal capsule. The tube was found to be generally useful for aspirating either gastric or duodenal contents.

\* From the Department of Physiology and the Gastro-enterological Section of the Department of Medicine, Jefferson Medical College, Philadelphia.

† Ross V. Patterson Fellow in Physiology and Gastro-enterology, Jefferson Medical College.



or for tubal feedings into either the stomach or duodenum Rehfuß in his recent book<sup>6</sup> describes the development of his tip in 1912 Gross,<sup>6</sup> Palefski,<sup>7</sup> Levin,<sup>8</sup> Lyon<sup>8</sup> and others devised modified tips also, but such improvements did little to revive the lagging interest in biliary drainage. The necessary stimulus was provided by Lyon<sup>10</sup> in 1919, who made successful clinical application of the idea after having read a footnote in a paper by Meltzer<sup>11</sup> two and a half years previously, suggesting that 25 cc of 25 per cent magnesium sulfate would relax the sphincter of Oddi as well as the duodenal wall and permit the bile to flow. Although based upon a "law of reciprocal innervation," for which evidence is lacking (cf. Ivy's review<sup>12</sup>), there is little doubt of normal relationship between relaxation of the sphincter of Oddi and increased gallbladder pressure not necessarily dependent on nerve pathways. However, this does not minimize the great step forward. Since that time there has been no especial improvement either in the technic of duodenal intubation or in methods of obtaining a dependable flow of bile. The studies have mainly been confined to learning which substances are most potent in their cholagogue effect.

#### TECHNIC OF PASSING THE TUBE

Confidence on the part of the operator is a definite prerequisite for successful passage of the tube. The patient must be put completely at ease. Time spent in first explaining and reassuring him may spell the difference between successful drainage of the gallbladder and failure. If there is likelihood of nausea, the throat may be painted with 1 per cent nupercaine solution, but in so doing the patient must be forewarned of the drying and numbing effect since its unexpected occurrence may make him more apprehensive. As the tube is swallowed, gagging may occur in spite of carefully repeated instructions. Without raising the voice, the operator directs the patient to cease swallowing and take several deep breaths of air through his wide-open mouth. The head must never be thrown back, but must be maintained in a normal position at all times. If, in spite of all precautions, revulsion occurs after two or three attempts, the patient should be sent home with instructions to take a sedative before retiring. The next morning the procedure may be repeated, and it is probable that with time to review his part and

with inhibitions lowered by the sedative he may be able to carry out the intubation without difficulty

When the tube reaches the lower pole of the stomach, usually at the 56-cm. mark, 8 ounces of warm water or saline are introduced through a funnel, and withdrawn immediately by gravity siphonage. Difficulty of entrance and evacuation of the solution may indicate that cardiospasm has prevented the tip of the tube from entering the stomach. This may be overcome by a few minutes' distraction, such as reading a newspaper or walking about. It is inadvisable to attempt complete recovery of the solution or to lavage further, since time spent here is unnecessary and is tiring to the patient. The tube may be clamped off or left open. The patient lies on his right side with his shoulder low and hips elevated so that the heavy tip will gravitate to the pylorus. He is then instructed to swallow easily at intervals so that at least twenty minutes are consumed in permitting the tube to advance 20 cm. At the same time, for psychic stimulation of peristaltic activity, he may imagine he is digesting some favorite food. Aaron<sup>18</sup> suggests pressure or percussion over the fifth dorsal vertebra, and tapotement (a tapping motion of the fingers on the epigastrium by rapid supination of the hands when the hypothenar eminences rest upon the abdomen), or the application of Credé's method of placental delivery to the stomach. Any of these methods may be useful in causing a stubborn pyloric sphincter to open. The patient should not be hurt or unduly excited, since any unexpected action may cause the stomach to relax.<sup>6</sup> A temporary change of position, even walking about, may permit the tip to enter the duodenum.

The correct position of the tip in the duodenum is best determined by fluoroscopy, but when this is not available a flow of viscid yellow bile is good evidence. A flow of turbid bile or of the neutral or alkaline contents means that the tip is in the duodenum but that it may still be in the cap, proximal to the ampulla of Vater, or may even have reached the jejunum. Auscultation upon injecting air is helpful but not too exact. There is no sure way of checking the position except by roentgen examination. The mere presence of bile should not be misleading. It is easily regurgitated into the stomach, but here the bile salts are precipitated and a sediment appears in place of the viscid material previously mentioned.

Care must still be exercised to prevent regurgitation of the tip into the stomach, which may occur from restlessness of the patient or, more frequently, with nausea due to retrograde movements of the duodenum which push the tip in a proximal rather than a distal direction<sup>14</sup> The patient should not talk during the entire procedure because of the nauseating effect of the tube in the throat A difference of opinion exists, however, and some may encourage the patient to talk to increase his confidence

Nevertheless, at this point particularly he should be oblivious to his surroundings and may sleep, read or listen to the radio It is advisable not to keep the patient intubated longer than necessary

#### OBTAINING THE SPECIMENS

The physiology of the mechanism for emptying the gallbladder has been studied extensively but still is imperfectly understood That the closing and opening of the sphincter of Oddi (the existence of which is now generally agreed upon) is important, is seen in all experimental studies on the pressures exerted by the secreting liver, gallbladder and the various ducts<sup>10, 17</sup>

Direct relaxation of the sphincter of Oddi seems of value, and *nitroglycerin*<sup>18, 20, 26</sup> has frequently been suggested for this purpose In my experience, however, this drug is inconsistent in reducing the spasm of the sphincter and too often permits the tip of the tube to fall back into the stomach, therefore I have discontinued its use

*Pavatrime* (B-diethylaminoethyl fluorene-9-carboxylate hydrochloride) in doses of 360 mg has yielded fairly good results It is believed to relax the duodenum and sphincter of Oddi When introduced through the tube into the duodenum there is usually a quiescent period of fifteen to twenty-five minutes, after which the "B" bile makes an abrupt appearance The color changes in the bile are gradual, the most intense golden brown occurring about twenty-five minutes after the first flow When the administration of the drug is successful the resultant formation of a fluorescent turbid yellow solution in the alkaline duodenum is apt to be confusing in the first collections of bile When pavatrime has not induced a flow of bile I have found that a magnesium sulfate-peptone solution seldom is effective either

In dogs the response to pavatrine is not the same as in the human subject. In ten experiments<sup>18</sup> a flow of bile was noted in only two, amounting to no more than 15 cc in either case, and the bile was not concentrated.

So far the substance found most effective in emptying the gallbladder is a mixture of *cream and egg yolk*, the stimulating effect depending on the fat content.<sup>21</sup> This does not excite the duodenum as much as olive oil— but has the disadvantage in common with all other media of mixing with the samples of bile.

In order to avoid contamination, I have allowed the tube to progress to the third portion of the duodenum or into the jejunum, introduced the stimulant followed by a little air, and then have withdrawn the tube until the tip reached the middle of the descending portion of the duodenum. The substances apparently act as well from the jejunum as from above, but it is not always possible to encourage the longer journey of the tube.

The next most effective substance is a solution of 5 or 10 per cent *peptone*. I have used *Bacto-protone* (a mixture of proteoses) in the same strength and prefer it, as with this preparation there is usually sharper delineation and more rapid collection of the gallbladder bile than with peptone. In controlled experiments on dogs having duodenal cannulas, a flow of concentrated gallbladder bile occurred within five minutes after installing 25 cc of 5 per cent *Bacto-protone* into either the duodenum or jejunum. Twenty-four experiments were performed with only one failure.<sup>19</sup> Two dogs were used in four additional experiments. One had a bisected loop of jejunum and an intact nervous system except for the divided myenteric plexus, the other had an intestinal anastomosis just above an ileal fistula, and was vagotomized and splanchnicectomized. The proteose solution was perfused through the loop and fistula. The latter animal gave no response to the stimulus while the former yielded a flow of bile similar in all respects to that of normal dogs. This could suggest that the stimulus is carried by way of extrinsic reflex pathways, but it may indicate simply that the ileum is incapable of cooperation. It is said that cholecystokinin is generated in the duodenum.

In the Curtis Clinic, we use a solution consisting of 20 cc of 7 per cent *peptone* and 10 cc of 50 per cent *magnesium sulfate*

with successful drainages in about 70 per cent of all cases. The magnesium sulfate tends to relax the sphincter of Oddi (but may fail if used alone<sup>15, 21</sup>) and the peptone is presumed to cause the gallbladder to contract. The completeness of evacuation is always questionable unless a dye-filled gallbladder is visualized by roentgen examination before and afterward. I am quite sure that it rarely empties completely.

#### SOME FACTORS INVOLVED IN EMPTYING

It appears important that the intubation should be begun early in the morning, since there is a psychophysical disturbance with increased duodenal irritability in most individuals whose breakfast is delayed. To effect a satisfactory drainage it is also important that the gallbladder be well filled, as it normally is after a twelve-hour fast. A full gallbladder exerts an increased pressure to insure a flow of bile. One should not be misled into wrong diagnosis on the basis of absence of gallbladder bile when the organ has not had a sufficient length of time in which to store up bile. The pressure of the bile in a well-filled gallbladder may influence its tone. A high tonus may be just as important in maintaining a sufficient pressure within the gallbladder as active contraction of the musculature during the emptying process. At any rate, Bainbridge and Dale<sup>23</sup> found that distention augmented tonus rhythm without causing contraction in anesthetized dogs, and Ivy<sup>12</sup> has never seen a good contraction in dogs in the digestive state with a partially emptied or contracted gallbladder. In addition, Deissler and Higgins<sup>27</sup> found that a certain optimum pressure was necessary in guinea pigs' gallbladders to produce normal tonus rhythm and that higher pressures would overcome the resistance of the sphincter of Oddi with leakage of the fluid.

Although the gallbladder is rather well supplied with fine nerve fibers and ganglia, present-day evidence suggests that these may exert a regulatory influence on tonus rather than initiate gallbladder contraction. That such tonus changes may be carried by nerve pathways would seem to be true from the experience of Boyden and Parmacek,<sup>24</sup> who frequently obtained a slight flow of bile on mere perception of fried bacon, or the observation of Levene<sup>25</sup> of a sudden increase in the size of the gallbladder during nausea.

We note that upon stimulation we do not always obtain a response in increased bile flow even when the gallbladder is fairly well filled. We may deduce that such a failure may be due to a low intraluminal pressure<sup>12 27</sup> which makes a stimulus ineffectual when it would be adequate if the tone level were higher. Of course it may be due to abnormal spasticity of the sphincter of Oddi. Because of this we should not be hasty in drawing the conclusion that there is obstruction due to other causes when we do not obtain a flow of bile.

#### EXAMINING THE BILE

Students always ask, "What should we look for?" The normal *color sequence* of the biliary drainage is *prima facie* evidence of a normally functioning biliary tract. The consensus among gastroenterologists is that the dark "B" bile comes only from the gallbladder. One may obtain a concentrated bile upon occasion in a cholecystectomized patient, but this would argue for a compensatory condition which is desirable. When "B" bile is present in only small amounts and with a relatively low concentration, it may be assumed that the gallbladder is functioning poorly. Complete absence of "B" bile is indicative of a blocked or non-functioning gallbladder. Absence of "A," "B" and "C" fractions must be due to complete closure of the common bile duct. Except in the last case, no one attempt is sufficiently conclusive for diagnosis. The degree of clarity or turbidity of the fraction is somewhat indicative of the state of the organs.

*Microscopic examination* only elaborates the picture of the color sequence. It reflects the condition of the part from which the bile originated. The examiner looks first for those particles usually present in disease of that part of the gall tract. The key to the anatomical structure from which the bile was obtained is in the type of desquamated epithelial cell which he views under the microscope, for example, the tall columnar cells which line the gallbladder serve as a check on the accuracy of recognizing "B" bile as coming from that structure. He further looks for pus, blood and crystals, especially cholesterol and calcium bilirubinate. In studying the pus cells, he notes whether they are bile-stained and whether they are degenerate, as these are clues to the extent of disease and the degree of stasis. He also examines the contents for parasites and bacteria,

making cultures in any uncertain case. In this latter connection, I might add that after careful mouth cleansing and with sterile apparatus the chances of obtaining an accurate culture are fairly good. When the same growth is found in two or three subsequent drainages and associated with other indications of infection, the evidence must not be ignored.

If roentgen study, such as the cholecystogram, is possible in conjunction with the drainage, four especially valuable details can be elicited in addition to what can be learned without it

- 1 Does the gallbladder fill well, and is it of normal shape?
- 2 Are there any calculi present?
- 3 Is the duodenal tube in the optimal position for drainage?
- 4 Does the emptying of the gallbladder as seen on the x-ray plates agree with the volumes and color sequence of the bile fractions obtained?

It is understandable that one may wish to perform a duodenal-biliary drainage when there are no radiographic facilities available. But it is not so justifiable, in my opinion, to make roentgen studies of the gall tract without a concomitant duodenal intubation, provided the latter is not specifically contraindicated by (1) acute infections of undetermined origin, (2) calculi liable to produce impaction, or (3) acute coronary or serious cardiovascular conditions.

#### CONCLUSIONS

Recent years have seen a shift away from biliary drainage as a therapeutic measure, it has come to be regarded only as a diagnostic medium. It is apparent, however, that there are toxic substances which may be removed only by periodic flushing of the biliary tract, and that the duodenal tube is an important adjuvant. In no other way are we as well able to follow the progress of our therapy. The benefit which patients with gall tract disease experience from periodic drainages cannot be fully ascribed to psychic reasons.

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## CONTRIBUTORS TO THIS NUMBER

Wright Adams, M D Associate Professor of Medicine, University of Chicago School of Medicine

Howard L. Alt M D , Assistant Professor of Medicine, Northwestern University Medical School, Attending Physician, Passavant Memorial Hospital.

Aaron Arkin, Ph D , M D , F.A C P , Professor of Medicine and Chairman of Department of Medicine, Cook County Graduate School, Associate Professor of Medicine (Rush), University of Illinois College of Medicine, Attending Physician, Cook County and Mt Sinai Hospitals, Staff, Wesley Memorial Hospital

Emmet B Bay M D , Professor of Medicine, University of Chicago School of Medicine

Robert S Berghoff, M D F.A.C.P., Clinical Professor of Medicine, Loyola University School of Medicine, Director of Heart Station, Mercy Hospital-Loyola University Clinics

Clarence F G Brown, M D Assistant Professor of Medicine, Northwestern University Medical School, Senior Attending Physician St. Luke's Hospital

Donald E. Cassels M D , Assistant Professor of Pediatrics, University of Chicago School of Medicine (Now Captain Medical Corps, Army of the United States )

I Davidsohn, M D , F.A C P , Associate Professor of Pathology (Rush), University of Illinois College of Medicine, Director of Department of Pathology, Mt. Sinai Hospital.

Ralph E. Dolkart, M D Instructor in Medicine, Northwestern University Medical School, Assistant Attending Physician St. Luke's Hospital

Gertrude Engbring, M D , Associate Clinical Professor of Medicine Loyola University School of Medicine, Associate Attending Physician in Medicine, Cook County Hospital

G K. Fenn M D Associate Professor of Medicine, Northwestern University Medical School, Senior Attending Physician, St Luke's Hospital

CONTRIBUTORS TO THIS NUMBER

- Angelo S. Geraci, M D , Clinical Associate in Medicine, Loyola University School of Medicine, Associate Director of Heart Station, Mercy Hospital-Loyola University Clinics (Now Major, Medical Corps, Army of the United States )
- N C. Gilbert, M D., Professor of Medicine, Northwestern University Medical Schools, Senior Attending Physician, St. Luke's Hospital
- Donald A. Hirsch, M D , Clinical Instructor in Medicine, Loyola University School of Medicine, Assistant Director of Heart Station, Mercy Hospital-Loyola University Clinics (Now Captain, Medical Corps, Army of the United States )
- Raphael Isaacs, M D , F A C P , Director, Department of Hematology, Michael Reese Hospital
- Joseph B Kirsner, M D., Ph D , Assistant Professor of Medicine, University of Chicago School of Medicine, Attending Physician, Albert Merritt Billings Hospital
- Louis R Limarzi, M D , Assistant Professor of Internal Medicine, University of Illinois College of Medicine, Associate Attending Physician, Department of Medicine, Research and Educational Hospitals, Consultant in Hematology, Henrotin Hospital
- Chauncey C. Maher, M D , Associate Professor of Medicine, Northwestern University Medical School, Attending Physician and Chairman, Department of Medicine, Cook County Hospital
- John Noll, Jr, M D , Major, Medical Corps, Army of the United States, Chief of Medical Service, Station Hospital, Chicago
- Walter Lincoln Palmer, M D , Ph D , F A C P., Professor of Medicine, University of Chicago School of Medicine, Attending Physician, Albert Merritt Billings Hospital
- John R Pepper, M D , Clinical Assistant in Medicine, Loyola University School of Medicine, Resident Pneumonia Service, Cook County Hospital
- Edith L. Potter, M D , Ph D , Assistant Professor of Pathology, Department of Obstetrics and Gynecology, University of Chicago School of Medicine, Pathologist, Chicago Lying-in Hospital
- Hildegard Schorsch, M D , Clinical Instructor in Medicine, Loyola University School of Medicine, Resident Pneumonia Service, Cook County Hospital
- Steven O Schwartz, M D., Attending Hematologist, Cook County Hospital

## CONTRIBUTORS TO THIS NUMBER

LeRoy H Sloan, M D, F A C P, Professor of Medicine, University of Illinois College of Medicine, Attending Physician, Cook County Hospital, Head of the Department of Medicine, Illinois Central Hospital

Don C Sutton, M D, Associate Professor of Medicine, Northwestern University Medical School, Attending Physician, Cook County and Evanston Hospitals

Italo F Volini, M D, F.A.C.P Professor of Internal Medicine and Chairman of Department of Medicine, Loyola University School of Medicine, Senior Attending Physician and Director of the Department, Mercy Hospital-Loyola University Clinics

Martin H Wendkos, M D, Captain, Medical Corps, Army of the United States, Instructor in Medicine, School of Medicine, University of Pennsylvania and Chief in Cardiology, Doctor's Hospital, Philadelphia (on leave), Chief of the Cardiology Section, Station Hospital, Chicago

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## SYMPOSIUM ON CARDIOVASCULAR DISEASES

### TREATMENT OF CORONARY THROMBOSIS\*

N C GILBERT MD†

I would like to spend the time at my disposal in a consideration of the treatment of coronary occlusion in general, without taking up any one case history. The diagnosis we will assume to have been correctly made, and we will assume it to be understood that coronary occlusion is a very different condition than angina pectoris, even though the nature of the pain is identical in each. If the diagnosis of coronary occlusion is uncertain, as it may be occasionally, it is much better to err on the side of safety. It is better to make the mistake of treating a patient for coronary occlusion, even though an occlusion has not actually occurred, than of not treating him for coronary occlusion. It is a mistake that would be made only rarely, for the next few hours or a day or so will usually determine whether or not an infarct has occurred.

#### IMMEDIATE TREATMENT

We should not wait hours or days to begin treatment. Treatment should begin at once, as soon as the patient is seen. Occasionally treatment is not adequate because patients "do not appear sick enough," or for one reason or another. One cannot

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\* From the Medical Departments of Northwestern University Medical School and St. Luke's Hospital.

† Professor of Medicine, Northwestern University Medical Schools. Senior Attending Physician, St. Luke's Hospital.

always tell from the symptoms just which case is serious and which is not. It is much better to risk a bad psychological effect than an effect which, if it is not homicidal, may produce a cardiac cripple.

Unfortunately, an impression exists among so many students and physicians that not much can really be done in the case of coronary occlusion, that some patients get well and some do not and there is little for the physician to do except to advise bed rest and nursing care. There are several very essential things to be done at once that make recovery more probable, and the after-effects less serious and less crippling.

A patient with a coronary occlusion is often not only in pain and distress, but is frequently extremely apprehensive in regard to the outcome. Emotional as well as physical rest is necessary. The necessary emotional rest depends a great deal upon the attitude of the physician, who must obtain the patient's confidence from the first. An indifferent or an obviously alarmed or uncertain doctor does not inspire the degree of confidence which is necessary to offset the psychological shock which accompanies the accident. Nor is a patient's faith in his own future welfare increased by a doctor who is ostentatiously busy, or who wears what Sproul has referred to as a "funereal air of wisdom." The case should be handled easily, quietly, confidently and surely. And it should continue to be handled with just as little fuss and feathers as possible.

As is true everywhere in the practice of medicine and surgery, it is necessary to review just what has happened, what the conditions are, their consequences, and what means we may have at our disposal to meet these conditions.

There is of course one all-important fact and that is the presence of the occlusion and the resulting infarct. You cannot alter the occlusion itself. That is done and it cannot be undone. You can, however, do some things to make the results of the occlusion less serious. These should be done at once, as soon as the case is seen, and include the immediate administration of atropine and a coronary vasodilator drug, and morphine or another opiate if necessary for the pain. As soon as the patient is in bed oxygen should also be given.

For a certain proportion of the patients, the accident will be immediately fatal. If the patient survives the immediate onset, he should be moved after the emergency medication to where

he can be cared for most easily, comfortably and adequately. Usually this means the hospital. He should not be moved again until complete recovery has taken place. When once the patient is in bed in the hospital or in his home he should have constant special nursing care.

### ATROPINE

When the occlusion occurs the body at once makes an effort to transport blood to the involved area by means of anastomosing vessels, extracardiac vessels in some cases, and very probably through other means of blood supply to the heart muscle, such as the luminal vessels and the thebesian veins.

At the same time, however, another event occurs which is very much to the disadvantage of the heart and its owner and offsets in part the efforts of the body to restore circulation to the involved area. This consists of a reflex vasoconstriction of the arteries in the uninvolved heart muscle. It increases the mortality rate and adds to the extent of the infarct and to the permanent damage done to the heart muscle in those who survive. In very large part it can be prevented and its prevention is important.

A few years ago, Manning, McEachern and Hall, and other workers in the Banting Laboratory in Toronto showed that when a coronary artery is occluded in the experimental animal there is at once a reflex vasoconstriction of the vessels in the uninfarcted myocardium, including the collateral arteries. This reflex vasoconstriction not only decreases the blood supply to the uninvolved heart muscle, but it hinders the efforts of the body to restore the circulation to the infarcted area. It adds to the probability of ventricular tachycardia and ventricular fibrillation and increases the extent of permanent damage and the probability of future incapacity. There are clinical reasons to assume that the same reflex vasoconstriction occurs in man. It is seen elsewhere in the body when an artery is occluded. If we keep in mind this vasoconstriction and its reflex nature, we are very sure that we can reduce the mortality.

The Toronto investigators observed that the death rate following ligation of the coronary artery in the dog was very low in the fully anesthetized dog. This has been confirmed in other laboratories. But if a ligature was placed loosely about the artery, and the dog allowed to recover completely from the anesthetic before the ligature was tied, the death rate was high. If



atropine was given at the same time that the ligature was tied or the vagi cut in the unanesthetized dog, the mortality was decreased to about that observed in the fully anesthetized dog. Bilateral removal of the stellate ganglion and the upper five thoracic ganglia also decreased the mortality to the same level as in the anesthetized dog. That it was some reflex mechanism responsible for the increased mortality in the unanesthetized dog was indicated by the effect of the atropine or vagectomy, and by the ganglionectomy. If they ligated one artery and measured the flow in an unobstructed artery, the flow in the unobstructed artery was found to decrease. That this was due to a reflex vasoconstriction and not to a fall in blood pressure was shown by the fact that it did not occur in the ganglionectomized dogs.

This work was repeated by LeRoy in our laboratory, with very similar results. By atropine alone he reduced his mortality from 70 to 50 per cent. This was not quite so great a reduction as Hall and his co-workers obtained, who reduced the mortality from 75 to 25 per cent, and to 10 per cent in the ganglionectomized dogs.

Since the work of Hall and his associates, we have used atropine routinely at once in all cases where the occlusion is at all recent. It is given in doses of  $\frac{1}{100}$  or  $\frac{1}{75}$  grain hypodermically. It has not been used intravenously because of unfavorable results observed a few years ago by C F G Brown following its intravenous use in experimental work. We have never seen significant increases in pulse rate or untoward results of any kind when atropine is given hypodermically. On the other hand, we have seen highly favorable clinical results as regards mortality and better progress during the recovery period in those cases in which it has been used in the first few hours.

I was much interested when talking to a physician in a small city to find that he had long ago made the clinical observation that patients with coronary occlusion to whom he gave atropine did very much better than others. For this reason he had used it routinely for years.

Relatively few patients enter a general hospital in the first few hours after a coronary occlusion. On our service, among thirty-five consecutive patients with definite history and findings and electrocardiographic changes who were seen in the first six hours, there were two deaths, or 6 per cent. One of these

at autopsy showed two old healed infarcts and was a cardiac cripple before the terminal infarct. The records of over half the patients we have seen on our service were lost when one of our number who was working on them was suddenly called to active duty in the Army. If we could include the lost records our percentage might be somewhat better but would be still statistically insignificant. Of course the next few cases might very materially alter the ratio one way or the other, but it is a much lower mortality rate than we had obtained previously.

Clinically, the atropine is given at once and repeated in four to six or eight hours, as indicated. Its use is discontinued as soon as conditions appear stabilized, which may be after the first dose or not until twenty-four to thirty-six or forty-eight hours have elapsed. We are usually able to discontinue its use after the first, second or third dose.

#### CORONARY VASODILATOR DRUGS

It would be supposed also that if a drug were used which would dilate the coronary vessels and increase the blood flow through the coronary arteries and their anastomosing vessels, there would be a better blood flow to the infarcted area, and the infarct would be smaller. There is ample experimental evidence to indicate that certain drugs do increase the coronary flow. Among these are drugs of the xanthine series, the nitrites, and papaverine. Smith and his co-workers showed that when aminophylline was given after the ligation of a coronary vessel in the dog, the infarct was smaller. Although some other investigators have not confirmed these findings, LeRoy took photographs in color of the infarcted area with and without the administration of a coronary vasodilator, and found the infarct smaller following the use of coronary vasodilators. Employing the same experimental procedure with dogs as in the atropine experiments, LeRoy reduced the mortality from 70 to 56 per cent by the use of aminophylline. Theobromine sodium acetate, although it is not suitable for parenteral use clinically, has a greater effect in increasing flow than does aminophylline. When it was used in the experimental animals, the mortality was reduced from 70 to 23 per cent.

It would appear from this work that drugs of the purine series are of definite value in the experimental animal, and we feel certain that this is also true clinically. A good indication of

this clinical value is the immediate cessation of pain in some cases following their administration alone. This result is understandable if they reduce the extent of the infarcted area, for the smaller the infarct the less the endocardial involvement and the less the probability of mural thrombi. We think also that they reduce the incidence of mural thrombi by reducing the extent of the infarcted area. The smaller the infarcted area, the less the endocardial involvement and the less the probability of mural thrombi.

*Aminophylline* may be used either intravenously or intramuscularly. For intravenous use the 10-cc or the 20-cc ampule, containing  $3\frac{3}{4}$  or  $7\frac{1}{2}$  grains, should be given, injecting the solution very slowly. Intravenous administration has the advantage of a more rapid action and the avoidance of the painful area which is apt to follow intramuscular use, but a disadvantage in that a fall in blood pressure may follow, especially if the solution is injected too rapidly. Other unpleasant symptoms may follow its too rapid injection, as palpitation, headache, nausea, or even precordial pain. On rare occasions a slight fall in blood pressure or palpitation may follow a slow injection, but such symptoms are never of sufficient importance to interfere with its use. When used intramuscularly, the effect of the drug is not so rapid, but it is more prolonged. A disadvantage is the pain, which may persist at the site of the injection for several hours. Much of this may be avoided by injection deep into the muscle. For intramuscular use, aminophylline comes in 2-cc ampules, carrying  $3\frac{3}{4}$  grains or  $7\frac{1}{2}$  grains.

There are other soluble salts of theophylline which are probably of equal value.

*Papaverine hydrochloride* is another coronary vasodilator of equal value with aminophylline. It has little or no hypnotic or analgesic effect and is not habit-forming. It can be given intravenously or hypodermically in doses of  $\frac{1}{2}$  to  $1\frac{1}{2}$  grains. For intravenous use, a dose of 1 grain should be sufficient. It also causes a fall in blood pressure, but I have never observed a significant fall to occur with either this drug or aminophylline. Morgan and Garr recently undertook a series of intravenous injections with each of the preparations, with especial reference to the effect on blood pressure. Aminophylline did not always cause a fall in pressure and occasionally caused a rise. The fall was always insignificant. Papaverine caused more of a fall than

did aminophylline, but never enough to be of consequence. The two drugs should never be used together, however, as under such circumstances a fall of serious consequence might result.

After the immediate emergency is over and the patient is able to take medicine by mouth, either of the preparations can be given orally. Papaverine should be used in doses of 1 to 1½ grains. Aminophylline or its equivalent theophylline preparation should be given in doses of 3 grains in enteric-coated tablets, or the insoluble calcium salicylate salts of theophylline can be used. The more insoluble any of these preparations are, the less likely they are to cause unpleasant symptoms, such as nausea or headache. The preparations insoluble in the stomach are absorbed readily from the intestine. There is no advantage in a readily soluble preparation for oral use. The acid stomach contents may precipitate out the alkaloid, and the absorption be the same as for the less soluble alkaloid. Or the stomach contents may buffer the acid of the stomach to the point where the alkaloid is not precipitated out, and the soluble salt absorbed by the stomach. If it is, there are more frequently unpleasant symptoms.

When drugs can be used orally, my own preference is for one of the *theobromine* preparations. The alkaloid theobromine has the advantage of carrying the full value of the active drug, and of being fairly insoluble in the stomach. It can be used in 5- or 7½-grain tablets or capsules. *Theobromine calcium salicylate* has the advantage of being relatively insoluble in the stomach and consequently is not likely to cause headache or nausea. It is absorbed readily from the intestines. It comes in 7½-grain tablets which should be given, one or two at a time, three or four times daily.

*Theobromine calcium gluconate* is another valuable salt, insoluble like the other calcium salts and, like them, less prone to cause nausea.

Of the soluble salts, *theobromine sodium salicylate* is the least valuable. It carries only 40 to 44 per cent theobromine and is the most apt to cause nausea. Unfortunately it is frequently used largely because of its easily remembered and readily written trade name of Diuretin.

*Theobromine sodium acetate* carries 60 to 66 per cent theobromine and probably the sodium acetate adds to its effect. It can be used in doses of 7½ to 10 grains, best in enteric-coated

tablets or in capsules The use of one of the drugs which increase the coronary flow should be continued all through the course of the treatment, three to four times daily, and for an indefinite later period

The nitrites are coronary vasodilators, but should not be used in coronary occlusion The marked fall in blood pressure which they produce may be sufficient to decrease the coronary flow in spite of coronary vasodilator effect There have been some fatal cases following nitroglycerin administration, and there might be more if the tablets of nitroglycerin used were more frequently of full strength Nitroglycerin tablets rapidly lose their full potency with age and exposure

*Caffeme* is a mild coronary vasodilator but has no value comparable to that of the other drugs

#### MORPHINE

Morphine, pantopon, or another narcotic should be given for pain, but it must always be given with at least  $\frac{1}{100}$  grain of atropine Hall apparently believed at one time that morphine might accentuate the vagus reflex affecting the uninvolved arteries, but later he decided it made no difference in this regard LeRoy leaned to the opinion that the use of morphine by itself, without atropine, tended to increase the mortality in experimental animals Morphine is best not used after it has relieved the first onset of pain.

#### OXYGEN

We are none of us clever enough to determine from the degree of shock, or the symptoms, or by physical examination or laboratory findings just how much damage has been done in any one case A patient may have very mild symptoms indeed, and no shock at all, and yet die of a ruptured infarct For this reason I think that not only should atropine and a coronary vasodilator drug be used in every case, but that oxygen should also be given, however mild the case may appear Any possible harmful psychological effect from the use of oxygen can readily be obviated by a simple explanation that it is being used not because the patient is so ill, but to prevent him from becoming ill and to make him more comfortable Furthermore, the attitude of the patient toward its use is much different than it was a few years ago, provided the physician is not too apologetic

about it. Oxygen desaturation in some degree is always present in this condition. If we can add just a little to the oxygen carrying power of the blood—not only to the oxygen carried by the red blood cells but to the oxygen carried in loose solution in the plasma—we may decrease the amount of damage done. That oxygen is efficacious is evidenced by the frequency with which the pain, the sense of oppression and the anxiety cease at once upon its use.

Occasionally, for some reason which I cannot even speculate upon here, an alkalosis may develop when oxygen is used and proceed to the point of symptoms. It occurs rarely, but should be watched for. We usually check the carbon dioxide combining power of the blood after twenty-four hours.

Oxygen is best administered by means of an oxygen tent. The tent is more efficient and more comfortable than other means. The temperature can be adjusted to meet the patient's needs, and on a hot day in a room that is not air-conditioned this is an important consideration. If a tent is not available, use can be made of nasal catheters or of one of the various masks. Neither of the latter methods is as satisfactory or as comfortable as a tent. The use of oxygen should be continued for one or two days or longer, until the pulse and respiration are approximately normal and the cyanosis is improved.

#### TREATMENT OF COMPLICATIONS

In some instances *auricular fibrillation* or *auricular flutter* may occur at the onset. Either is best controlled by the regimen outlined and if it persists, as it does rarely, other treatment, which will be considered later, may be necessary. *Premature ventricular contractions* frequently occur, but do not of themselves require anything in the way of treatment. They may originate in an irritable focus present in the ventricular muscle before the coronary occlusion occurred, but usually they are an expression of increased irritability of the heart muscle due to insufficient blood supply and are best treated by continuing the aminophylline or papaverine and oxygen in adequate dosage.

*Ventricular tachycardia* is a constant succession of such premature ventricular contractions. It is a most serious complication and may eventuate in ventricular fibrillation and death. It is not likely to occur when atropine is used at once and aminophylline or papaverine and oxygen are employed.

Quinidine is frequently used in coronary thrombosis for the purpose of preventing ventricular tachycardia and the frequent ventricular fibrillation which follows. Quinidine has been shown to decrease the probability of ventricular tachycardia and fibrillation in the experimental animal when a coronary artery is ligated, which it does through its depressant effect upon muscle irritability, but it is to be remembered that it depresses the other functions of the cardiac muscle as well. It has been shown to cause the very condition for which it is used. We have seen untoward effects from its use, and do not employ it. It certainly should not be used routinely.

*Heart block* may occasionally occur, but this is not serious of itself unless too much attention is paid to it therapeutically. Again, aminophylline or papaverine is best for prevention and best for treatment if it does appear. Barium chloride should not be used. It reduces the coronary flow and causes an increased irritability of the heart muscle probably by reason of an increased ischemia. I see no reason for the use of magnesium sulfate intravenously or for giving potassium salts.

*Shock* is largely the result of circulatory insufficiency. It is absent or transitory when treatment is begun at once, except in the unusually severe cases with very extensive initial damage. Intravenous saline or glucose should not be used and I see no necessity for giving plasma or for transfusion. There are contraindications to the use of peripheral vasoconstrictor drugs. Blood pressure should be left where it is and not tinkered with. A return to previous higher levels is a good sign.

*Edema of the lungs* sometimes occurs when treatment of the occlusion is begun late, and may occur when treatment is begun at once. It is best cared for by one of the milder mercurial diuretics, used carefully. It is advisable to start with a small dose and avoid too free a diuresis. Hypertonic glucose will help the edema, but is best not used for the same reason that saline or glucose solutions are not employed intravenously in this disease. In a normal person under normal conditions, the use of such solution would make very little difference in blood volume, for as rapidly as fluid was taken into the blood stream, the excess would be eliminated by the kidneys. But where there is a decreased minute volume of blood being delivered by the heart, and a decreased volume flow through the kidneys in consequence, one would expect the blood volume to be increased.

Murphy has shown clinically that cardiac patients may be made worse by such solutions intravenously

I see no reason why *digitalis* should be used routinely and several reasons why it should not be employed at all early in coronary thrombosis. Occasionally in late cases it may be necessary. One does not wish to slow the pulse per se, and if one did wish to do so, *digitalis* would probably not do it. The pulse rate is usually best just where it is, if a normal mechanism is present, it will find its own optimum level. Atropine, a vasodilator drug, and oxygen will best care for the pulse and its rate by supplying more blood to the heart muscle. One certainly does not wish to increase the conduction rate. Contractility is best cared for by an increased blood supply to the heart muscle. Tonus is best left to the discretion of nature, for a longer muscle fiber may be a mechanical advantage. And irritability of the heart muscle, of all things, one does not wish to increase, for such an increase may result in ventricular tachycardia and ventricular fibrillation, which we are doing our best to avoid. We also feel that in full doses *digitalis* may cause coronary vasoconstriction. Laying aside all such considerations, there is no dearth of instances where patients have been made worse by its use.

Auricular fibrillation, when it occurs at the onset of the attack, usually ceases within a short time. If it persists, and if the heart rate is so rapid as to result in passive congestion, *digitalis* will have to be used to control the rate. In cases of passive congestion with a normal mechanism which occur later during the recovery process, *digitalis* can be used, preferably in small dosage. One must be ready to discontinue it if the output of urine does not increase or if the output becomes less. We prefer to get along without it if possible—and it almost always is possible—and to use mercurial diuretics for the edema. This is not because we do not like *digitalis*, but because we like it so much—in its proper place.

For *restlessness and sleeplessness*, recourse may be had to the milder barbiturates. We use phenobarbital almost routinely all through the period of bed rest and frequently beyond it. It is given in small doses, such as  $\frac{1}{2}$  grain at night and  $\frac{1}{4}$  grain in the morning. Such a dose decreases restlessness and is usually not enough to cause drowsiness. Larger doses can easily be used if necessary. If something additional is advisable for sleep, one



of the more rapidly acting and rapidly eliminated barbital derivatives can be used

Patients who have coronary accidents very frequently also have *spastic colons* and *spastic constipation*. The physician should make sure that the patient gets enough drinking water, especially the first thing in the morning, and he may prescribe one of the heavier mineral oils, or an emulsion of oil and agar. Such emulsions should not contain cathartic drugs. Solid white vaseline by mouth is not difficult to take, and does not have the unpleasant by-effects of the lighter oils. Mineral oils should always be taken before sleep at night and upon awakening in the morning, and never at or near meals. If cathartics are necessary, the mulder saline cathartics should be used and not the strong stimulating cathartics. Small doses of phenobarbital are very helpful in cases of spastic constipation. If necessary they can be combined with small doses of belladonna or one of the newer preparations which have an atropine-like action.

A similar regimen of diet and phenobarbital and belladonna, combined with the bed rest indicated in coronary occlusion, will be helpful if *duodenal ulcers* are present. Mucin may be used. Any more active treatment, such as alkali therapy, is practically never necessary. Gas and distention are not at all apt to prove of much consequence with the care of the diet and bowels already described. If necessary, enemas may be used for immediate relief.

Occasionally a patient may have a *hiatus hernia* which will usually respond to the same treatment as does the duodenal ulcer. A patient with hiatus hernia should be permitted to choose his own position in bed, and if he wishes to be in a semisitting position, or propped up, his wishes should be followed.

*Diabetes* should be treated adequately as diabetes, with insulin when insulin is necessary. But the insulin should be used in doses that permit a little sugar to show in the urine and permit the blood sugar to remain high enough to provide an adequate bulwark against a possible hypoglycemia, which would not only be uncomfortable but would be disadvantageous to the heart.

*Pulmonary emboli* call for the immediate use of atropine hypodermically and papaverine or aminophylline intravenously. As shown by de Takats and his co-workers, this decreases the mortality materially. *Peripheral emboli* may occur at any time from the first to the eighth week and possibly later, but we have

seen none in the cases that have been treated immediately. With peripheral emboli the question of embolectomy arises. Whether embolectomy is advisable will depend upon the patient's general condition, which is usually good since emboli usually occur late, and upon the nature and extent of the damage caused by the embolus. No chance should be taken on a possible amputation. In the case of *cerebral embolism* we are more helpless. Here again there is probably a halo of vasoconstriction about the embolus, causing a decrease in blood supply and adding to the damage. We have tried injection of the stellate ganglion in order to offset this vasoconstriction only once and the results were satisfactory in that one case. Oxygen might presumably help by enabling the blood to carry an additional supply to the area of the embolus. How much it helps we do not know, but we use it.

I see no especial point in the use of heparin or dicumarol in the ordinary case. If thrombosis occurs, neither drug should be expected to affect a clot already formed, and if the occlusion is due to another cause, as a subintimal hemorrhage, there is again no reason for assuming that either will help. On the other hand, in cases with a decreased coagulation time and in which the heparin curve, described by de Takats, is flattened, the possibility of an extension of the thrombus might be anticipated, and one of these drugs, preferably dicumarol, would be expected to be of value. The heparin curve is very easily obtained at the bedside.

A minor but uncomfortable complication at times is the occurrence of *stiff and painful joints*, involving especially the shoulder. This may be the consequence of prolonged bed rest from any cause. We have tried mild physiotherapy, such as light massage, passive motion, and heat, in two or three cases with favorable results, and we shall continue its use.

#### NURSING AND GENERAL CARE

There should be no hard or fixed rule about *bedside company*. It is best restricted, but care must be taken that too rigid restrictions do not make the patient more restless and apprehensive. There should always be a special nurse if possible, and the question of company and its length of stay can be left to her judgment.

All patients, both male and female, should use the bed pan, and not get out of bed. In exceptional instances men who make

hard work out of the use of a bed pan may be permitted a commode beside the bed

The *diet* should be barely sufficient for the daily caloric needs, easily digestible, and adjusted insofar as possible to the patient's wishes and tastes. It should maintain the blood sugar at high normal values, furnish sufficient protein, and not be such as to cause gas. Dietary management is more of a quantitative than a qualitative problem, the more food, the higher the metabolic rate and the greater the work for the heart.

Questions often arise regarding the use of *coffee*, *alcohol* and *tobacco*. I see no reason why coffee should not be allowed if it does not increase restlessness. The patient may be made more comfortable with it. The use of alcohol is a matter of individual judgment. It is of little therapeutic value but may be allowed in moderate quantities if the patient desires it. Tobacco is best omitted unless such omission causes actual restlessness, and even then its use should be very limited. Even in habitual smokers it may cause a decrease in coronary flow, especially when used on an empty stomach.

The duration of *bed rest* is a matter of judgment in each case, but it should never be less than eight weeks. The danger of emboli from mural thrombi is not over in four weeks, or six, or even eight, nor is the heart ready to resume its full duties so soon. Following bed rest, activity should be resumed gradually. Just how gradually will depend upon the response which is experienced when the patient is allowed up for short periods. Certainly an extra month should be allowed for convalescence after the period of bed rest, even in the most favorable cases.

#### COMMENT

I would suggest that the reader himself review the experimental work on coronary thrombosis from Hedblom to the present time, and the clinical results from Askanazy to the present time. This is better than accepting uncritically reviews which have been edited to the point where they are not altogether impartial.

Drugs such as aminophylline or papaverine, which frequently cause the pain of a coronary thrombosis to cease at once and favorably influence the course of the disease, and which quickly relieve pulmonary edema and paroxysmal dyspnea, must be of rather definite value. I would certainly wish one of them to be

used if I were the patient. When these drugs are used by mouth in angina pectoris, a great many people, including physicians, are able to carry on their usual duties in comfort who could not do it otherwise. There may be some doubt as to the exact manner in which the purine base diuretics and papaverine act to increase the coronary flow. They are not going to "cure" coronary thrombosis or angina pectoris, but they are valuable aids.

I think that the doubt expressed in certain quarters concerning the value of these drugs is a serious matter. Their use may mean the difference between life and death, between complete and only partial recovery, between invalidism from anginal pain and resumption of a normal life. This expressed doubt is especially unfortunate if it influences students who have not yet acquired sufficient critical background. It is not as serious as regards those clinicians who are taking personal care of their own patients and learn by clinical experience the value of these drugs.

## ANGINA PECTORIS\*

G K FENN, MD†

### HISTORICAL BACKGROUND

EIGHT years before the Declaration of Independence was signed in Philadelphia, the Illinois country, which included Chicago, had recently been transferred from French to British control. Captain Thomas Sterling, on behalf of the British, took possession of Fort Chartres and the Illinois country in 1765. In 1768 the command passed to Colonel John Reed of the British Army. This historical reminiscence will serve to sketch in the local background of the year 1768, in which an English physician named William Heberden published a paper in the *Medical Transactions of the College of Physicians*. The title of this paper was "Pectoris Dolor" and in the course of it Heberden says, "But there is a disorder of the breast marked with strong and peculiar symptoms, considerable for the kind of danger belonging to it, and not extremely rare, which deserves to be mentioned more at length. The seat of it and the sense of strangling and anxiety with which it is attended, may make it not improperly be called angina pectoris." Thus was the label attached to the subject of our discussion this morning.

The pain of angina pectoris had been known before Heberden's time and had been previously described. Indeed, some of the best descriptions had been from the pen of lay persons. Seneca, whose life spanned the birth of Christ, and who wrote very bad tragedies in very good Latin, described his own anginal pain with great clarity. The Earl of Clarendon, in the seventeenth century, described the pain *in the left arm* suffered by his father, Lord Clarendon. He says, "he was seized on by so sharp a pain in the left arm for half a quarter of an hour, or near so much, that the torment made him as pale (whereas he

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\* From the Medical Departments of Northwestern University Medical School and St. Luke's Hospital.

† Associate Professor of Medicine, Northwestern University Medical School, Senior Attending Physician, St. Luke's Hospital

was otherwise of a very sanguine complexion) as if he were dead, and he used to say, 'that he had passed the pangs of death, and he should die in one of those fits' " He did

It was Heberden, however, who placed this disorder before the medical profession as a distinct clinical entity and who gave it the name it bears today

Now then, Heberden and his colleagues, among whom were Jenner, Hunter and Fothergill, thought that this disorder had something to do with the coronary circulation. It is popularly reported that Heberden did not mention the coronary circulation in his original report because he did not wish to worry his friend John Hunter, who suffered from anginal attacks. Hunter, however, seemed to be under no misapprehension about his trouble. He stated at one time that "my life is in the hands of any rascal who wishes to worry and tease me " He demonstrated the truth of this observation by dying suddenly at St. George's Hospital just after a rather acrimonious session with some of his colleagues. This rather ill-defined relationship to the coronary circulation was not made clearer by Heberden's paper in which he said, "On opening the body of one who died suddenly with this disease, a very skillful anatomist could discover no fault in the heart, in the valves, in the arteries or in the neighboring veins "

The ill-understood relationship between the coronary circulation and anginal pain caused all breast pain of this type to be called angina pectoris, and it was not until 1912 that our fellow-townsmen, James B. Herrick, taught us how to distinguish the pain caused by coronary occlusion and to make a diagnosis of coronary occlusion under the proper circumstances. In his article, Herrick removed a large number of patients from the general collection of those suffering from breast pain and placed them in a special group. Henceforth this group shall be known to suffer from coronary occlusion. In the present discussion the term angina pectoris will *not* be applied to those patients suffering from coronary occlusion.

#### THE ORIGIN OF ANGINAL PAIN

It seems obvious that anginal pain is related to the coronary circulation. It seems equally obvious that all anginal pain is not due to the same sort of coronary artery disorder. For instance, it is quite possible to have anginal pain with a relatively normal

coronary circulation In view of the fact that most anginal pain occurs after the age of forty-five years, it goes without saying that most anginal pain is associated with some *coronary artery change* However, in many cases the anginal pain must be predicated upon things other than the changes in the structure of the coronary arteries In the days when we saw very low red cell counts and low hemoglobin percentages in *pernicious anemia*, anginal pain was a common symptom of this disease Nowadays when the red cell count and the hemoglobin are usually maintained at normal or near normal levels, anginal pain is much less frequently observed It still occurs occasionally as a symptom of severe anemia Here, of course, the coronary vessels are not entirely at fault The impoverished blood is an important factor Likewise, one may encounter a *diabetic* in whom anginal pain occurs as the result of hypoglycemia The usual story is that the patient seems to be well controlled by insulin No sugar appears in the urine Upon questioning it develops that anginal pain is relieved by food The patient feels fine following meals. Further investigation reveals low fasting blood sugar levels Here again, it is not the structure of the coronary vessels that is primarily responsible for the pain It is the quality of the medium that is passing through them

Anginal pain may sometimes occur in association with marked *hypotension* One must remember that the coronary flow is a function of the mean blood pressure It is entirely conceivable that the blood pressure may at times be so low that a sufficient coronary flow is not available These represent a few examples of the occurrence of an inadequate coronary flow with a normal or relatively normal coronary vascular system

A rather unique situation lying somewhere between the foregoing and the frank coronary artery disorders is encountered in some cases of *hypertension* with left ventricular hypertrophy Anginal pain is usually a rather late manifestation in hypertension Its occurrence ordinarily signifies the appearance of structural changes in the coronary vessels This, however, is not always true In certain instances the muscle mass of the left ventricle increases rather rapidly to compensate for the additional load interposed by the hypertension The coronary circulation increases with the blood pressure up to a certain point and thus the increasing pressure carries its own compensatory increase in coronary flow At certain levels of cephalic pressure

the coronary flow becomes reflexly inhibited. We are then confronted with a situation in which an increased muscle mass cannot receive an adequate blood supply even though the coronary vessels are relatively normal. The coronary circulation cannot increase in the number of vessels. In addition, the coronary capillaries, which lie between the muscle fibers, have been stretched out by the muscle hypertrophy and dilation and this stretching tends to reduce the lumen of the capillary. Thus we have a normal, or relatively normal, coronary circulation which is unable for at least two reasons to meet the demand placed upon it by an increased cardiac muscle mass. And so it is that anginal pain may occur in such cases without the necessity of seriously damaged coronary vessels.

Mention of the cephalic inhibition of the coronary flow opens the question of *reflex inhibition* of the coronary flow in general. For a long time it was not admitted that the coronary vessels might undergo active constriction, or dilatation either as far as that is concerned. This is no place to enter upon a discussion of whether or not the coronary flow may be influenced by things other than blood pressure and cardiac work. That discussion has already filled many, many pages in the medical literature. Those of us, however, who have insisted that active coronary vasoconstriction and reflex vasoconstriction was a fact believe that a great weight of evidence is piling up to support us. Evidence has been brought forward to show that stimuli in at least three different places are capable of producing reflex coronary constriction. It is altogether likely that other sources for this reflex constriction exist.

A few years ago Hall in Toronto and LeRoy in our own laboratory showed the presence of reflex coronary artery constriction resulting from acute coronary occlusion. This work seemed quite conclusive and has modified our treatment of acute coronary occlusion. At about the same time, de Takats, Beck and I published some work that showed the occurrence of reflex coronary constriction associated with pulmonary embolism. Sometime later Gilbert, LeRoy and I demonstrated experimentally that the coronary flow may be greatly reduced by distention of the stomach. This work was carried over to the human where it was shown that anginal pain came on much more rapidly and easily when the stomach was distended and that this phenomenon might be prevented by breaking up certain re-



flexes All of this has been published at considerable length and need not be discussed now, but it convinces us that stimuli arising in various parts of the body are capable of producing reflex coronary constriction and that these reflexes added to an already impaired coronary flow may be responsible for anginal pain

In addition to those stimuli mentioned here there are doubtless many others that produce constriction of the coronary vessels in one way or another *Emotional stress* is notorious in this regard There is no doubt that the *smoking of tobacco* produces appreciable coronary constriction in some persons Altogether there are many things apart from structural change that may produce a reduction of the coronary flow in a susceptible individual

Now then, I distinctly do not want to leave you with the impression that I believe that most anginal pain occurs without structural change in the coronary circulation It is true that most persons suffering from anginal pain have a disorder of the coronary arteries The coronary artery disease itself many times produces the anginal pain but the other factors that I have mentioned often enter into the picture The anginal pain caused by obstructive changes in the coronaries has certain distinctive characteristics that I shall discuss in a moment At this point I wish to call your attention to certain cardiovascular disorders that produce a pain that is often confused with the pain of angina pectoris

*Aortitis* produces substernal pain that is very similar to that produced by coronary artery disorders It is a burning pain that may have the same location and radiation as the pain that we have been discussing Yet for purposes of this discussion, at least, aortic pain must not be confused with true anginal pain It was not so long ago that most anginal pain was attributed to aortic causes, and Sir Thomas Clifford Albutt rather scornfully called the adherents of the coronary artery theory the "coronarians" In this category comes also the pain of aortic insufficiency

The *rupture of a dissecting aneurysm* may cause pain that is very difficult, if not impossible, to differentiate from pain of coronary origin This event is more likely to be confused with a coronary occlusion than an attack of angina pectoris but the pain element is the same *Pericarditis* may for a time be confused with anginal pain

There are, of course, a host of pains of noncardiac origin that

may be confused with anginal pain but there is no time to discuss that phase of the subject here. It is well to remember, however, that all chest pain does not have its origin in the coronary circulation.

### CLINICAL PICTURE

#### Angina Pectoris

Now that we have dealt with the origin of anginal pain it might be well to discuss the pain itself. It would seem almost unnecessary to describe the pain of angina pectoris when it has been done so many times but we must try to differentiate the several varieties of anginal pain as well as we can in order to have a logical approach to the management of each case. For the purpose of this discussion let us say that the term *angina pectoris* is applied only to a certain variety of anginal pain. That variety is the sudden attack of breast pain that comes on without much warning and is very severe indeed. The patient is seized with an attack of pain that is located beneath the sternum usually at the junction of the lower and middle third. The pain comes on suddenly and reaches its full development almost immediately. The patient has no time to do anything but stop where he is and seize upon the nearest object for support. The pain may be and usually is referred to the left shoulder and down the left arm. It goes down the inner aspect of the arm and may extend into the middle and ring fingers or it may terminate abruptly at the inner aspect of the elbow. Rather frequently the pain is referred to both shoulders and arms, and sometimes it may go to the right side only. It is not infrequently referred upward to the neck and the jaws and it may cause a sensation resembling toothache. Much less frequently it is referred into the back at the base of the neck. Very rarely it may be felt between the scapulae. It may also be referred downward but with much less frequency. When the pain is referred downward toward the abdomen it is sometimes difficult to differentiate the entire episode from an attack of upper abdominal pain. It seems to me that this variety of angina is particularly important because it is so likely to be overlooked and attributed to an abdominal disorder.

Together with the pain there is a *sense of constriction* in the chest. This has been described as a viselike pressure or a sense of fullness that resembled a pressure from within. There is also

a certain *feeling of apprehension* that does not accompany other varieties of pain. This sense of apprehension has received a number of titles among which "the icy hand of death clutching the heart" and "a sense of impending dissolution" are perhaps the most descriptive

The pain with its attendant phenomena comes on as described, lasts a varying period of time usually not exceeding fifteen minutes and then subsides as quickly as it came. During the attack the patient remains perfectly quiet. He seldom makes a sound. His breathing is slow and shallow. Dyspnea is no part of this attack. It seems that the patient voluntarily inhibits his movements from fear of greater pain as a result of movement, even breathing. During the attack the patient's face is gray, a mixture of pallor and cyanosis. His lips appear blue and he looks very ill indeed, as he is. With the subsidence of the attack the patient takes a long breath, slumps back relaxed in his chair, perhaps smiles and apologizes and except for a great exhaustion he seems to feel quite well.

This is a typical attack of angina pectoris. It is a burning, chest-filling pain, with a sensation that the ribs are being pressed into the chest and a sensation that every breath may be the last. With the subsidence of the attack, no signs are left behind. There is no change in the blood pressure or pulse, no physical signs that would indicate that a serious crisis had just been passed. It is important to remember this, since often the aftermath produces the only evidence to differentiate such an anginal attack from an occlusion of a coronary artery. It is my opinion that the attack just described is always precipitated by an active constriction of the coronary circulation. This is not to say that such attacks frequently occur in the absence of coronary artery disease. Not at all. A pathologic change in the coronary artery is usually present but still the determining factor in the attack is that of active constriction of the coronary vessels.

#### Angina of Effort

When marked coronary artery disease is present, one is likely to see a different type of anginal pain. This is the pain that begins almost exclusively with exercise and builds up rather slowly. The patient notes the pain as he walks along the street and he knows if he goes too far it will become quite severe. BUT, he is able to go along until the pain slowly reaches a cer-

tain point in severity and then he may stop and rest for a time and the pain slowly subsides. Thus by exercising and resting alternately, he may carry on fairly well. In other words, he has the pain more or less under control and he is able to escape severe attacks by watching his behavior. This type of pain is the result of an insufficient coronary circulation, either functional or organic, and is quite different from the attack of angina pectoris that was previously described.

### Atypical Anginal Pains

We must also consider the somewhat atypical pains that point toward a coronary origin. Lord Clarendon spoke of his father's pain which was confined to the left arm only. As a matter of fact, the pain may be confined to any of the areas of reference and may be of any degree of severity. We must therefore carefully investigate all of the pains in this locality that occur in individuals of a certain age group and determine whether or not these pains may be of coronary origin. Pain any place in the chest or arms that has this peculiar squeezing character and that is predicated upon exercise must be investigated for a coronary origin.

### Illustrative Cases

It is difficult to present before the clinic an example of angina pectoris, for it is seldom that the patient times his attack to coincide with the hour of the clinic. Only once in many years of teaching has the attack occurred at the proper time. I have one or two records that I exhibit rather frequently to demonstrate some of the things that we have talked about.

A. P., a gentleman aged sixty-six years, first came to me because of pain in the left shoulder and arm. He operated a small machine shop where he specialized in the repair of automobile carburetors and generators. His office was situated on a balcony above the work floor and he noted that when he went up and down the stairs to his office too frequently he developed a pain in the left shoulder and arm. He had assumed that this pain was due to a local disturbance in the shoulder and he had discovered that if he immersed his arm in hot water the pain usually subsided. He confessed, however, that if he merely sat down and waited the pain disappeared in a few minutes anyway. He also had attacks of the same sort when he was driving his car in heavy traffic and became irri-

tated by his inability to move along rapidly. When the attack came on under these circumstances he stopped his car at the earliest opportunity and waited for the pain to pass.

I was very curious about the relief he obtained from immersion of the arm in hot water but he insisted that there could be no mistake about it and that he kept a pan of water heated in his shop exclusively for this purpose. I was quite convinced from the history and from the location of the pain that I was dealing with an anginal affair. I could not see, however, how the local application of heat could be effective in stopping the pain. It occurred to me, however, that this immersion of the arm in hot water might provoke a general vasodilatation and thus relieve the anginal pain. I suggested that next time he immerse his right arm in the water and observe the effect on the pain in the left arm. He saw no point in this procedure but he agreed to undertake it just to humor me. To his great surprise it worked just as well as the immersion of the left arm. This then was a case of moderately severe anginal seizure that was relieved by rest and by heat. Later under appropriate management these attacks were reduced materially in number and severity.

About a year after this gentleman came under my observation he had an unusually severe attack of pain one afternoon at the shop. Immersion of the arm in water, nitroglycerin under the tongue and other measures failed to have any effect on the pain. Instead of subsiding in ten or fifteen minutes it lasted for three hours in such a severe form that he was unable to get home. When he did arrive at home some three or four hours after the onset of the pain he became nauseated and vomited. His pain still continued but was less severe. He stated that the pain was almost identical with that from which he had suffered for the past months. It extended slightly more into the chest and was more violent than most of his previous attacks. I sent him to the hospital, of course, as soon as my attention was called, and subsequent examinations proved that he had suffered a coronary occlusion.

Here then was a man who had suffered numerous attacks of anginal pain without anything more than temporary disability. The same sort of pain with certain modifications and sequelae proved to be the principal symptom of a coronary occlusion.

R. H., a man of fifty-eight and an executive in a highly competitive insurance business, began having attacks of substernal distress that were brought on by rather moderate exercise. He noted that he could no longer walk from the station to his office, a thing

that he had done for years without trouble. He has never had a crushing anginal attack but very uncomfortable anginal pain followed upon every attempt to get actively about. After this had been going on for about a year he took a six-months' holiday and went abroad to visit his daughter. Very soon he found himself doing things that he would not dream of attempting at home. Soon his anginal pain had virtually disappeared and it took a great deal of exercise to cause him to feel it at all. Naturally, he was delighted, only to be greatly disappointed when his symptoms promptly reappeared when he returned home and resumed his work. This seems to me to demonstrate the effect of emotional stress in promoting painful episode of this sort.

I could go on indefinitely presenting case records to show the variable nature of this disorder and the different forms under which it appears, but perhaps we should now approach the discussion of what to do about it.

#### MANAGEMENT

Nothing in the field of medicine requires a more careful individual study than does the case of angina pectoris. First, we must be sure of the diagnosis. Almost everyone nowadays realizes the seriousness of a diagnosis of angina pectoris and we must be careful not to subject our patient to the mental burden of this diagnosis unless we are sure of our ground. Secondly, the general management and the specific treatment are greatly influenced by the correctness of the diagnosis.

#### General Measures

When the diagnosis seems to be definitely established it becomes the duty of the physician to determine, if possible, what sort of anginal pain he is dealing with. Is it effort alone that produces the distress or is it the pressure of business or emotional stress? Or is it a combination of several contributing factors? It is necessary of course, to greatly *modify the habits* of the patient in many instances and a study of the immediate causes of his anginal pain is the most important guide to the modification. Unless the patient is engaged in an occupation that requires hard manual labor, it is surprising how frequently he can carry on his usual occupation with certain modifications. Perhaps it will be necessary to shorten his working hours, frequently short vacations not too far apart will work very well.

Avoidance of controversial subjects and avoidance of any activity or occupation that causes emotional stress must be insisted upon. In other words, the patient may play golf if he does not take his game too seriously. The same applies to bridge or to attending football or baseball games or even to listening to the radio under certain circumstances. A careful study of the entire situation will often show how the attacks may be greatly reduced. A patient may be able to do a certain amount of exercise in the summer that is impossible in the winter. It is well known that many attacks are precipitated by breathing cold air. The same is true of exercise before and after meals.

This brings me to a discussion of the relationship of the *gastro-intestinal tract* to the occurrence of anginal pain. It is well known that anginal attacks occur more frequently following meals and in the presence of gastro-intestinal disorders. It has now been shown that distention of the stomach and bowel, either by food or by gas, causes a sharp reduction in the coronary flow and causes anginal pain to come on with less provocation. Therefore, as a general proposition, the gastro-intestinal tract should be kept in good order. Any tendency toward constipation should be overcome. A study of the patient's peculiarities will show what foods he does not tolerate well. The known gas-formers should be avoided. And above all the patient should avoid any provocative activity after meals. Indeed, he should avoid large meals.

*Mental tranquillity* is of great importance in dealing with anginal pain. We are all familiar with the greater prevalence of anginal attacks during periods of financial crisis or during an election year or even in wartime. Of course it is not always possible to achieve mental tranquillity. We cannot, apparently, avoid having financial depressions occasionally and we do not want to avoid election years. We can attempt to keep our patients out of many emotional crises and we can teach the patient to avoid too much mental excitement. It is surprising how much a bit of self-control will accomplish. When the patient is taught that he *cannot afford* to get angry or that he *cannot afford* to argue about trivial subjects, his life becomes very much more tranquil. The patient must realize that violent argument accomplishes very little anyway except to precipitate anginal attacks in susceptible individuals.

## Treatment of the Attack

After we have studied the patient carefully to determine what general management to apply to his case we come to the matter of administering drugs. For the treatment of the attack, *nitroglycerin* under the tongue has no serious competitor. We still find most sufferers of this disorder carrying the small vial of hypodermic tablets of nitroglycerin, grain  $\frac{1}{100}$ , in his pocket. One of these placed beneath the tongue will ward off most attacks or at least shorten the duration. This dosage may be repeated frequently without apparent danger, but to assume that unlimited amounts of nitroglycerin are quite innocuous is a mistake. It does lower the blood pressure to a considerable degree and when this effect is pushed unduly, ill effects may result. Inhalation of amyl nitrite from the well known amyl nitrite pearl is almost as effective as nitroglycerin but it is perhaps slightly more dangerous. These remedies are so well known that I need not talk further about them here.

As a general rule, *narcotics* are in the class of bad treatment for attacks of angina. The attacks occur too frequently and in any event if the pain persists long enough for the physician to arrive and prepare and give a narcotic one should doubt the diagnosis.

## Drug Prophylaxis

The next task is to attempt to forestall the attacks. As already pointed out, prevention is first a matter of management rather than drug treatment, but unfortunately it is impossible to "manage" away most attacks of angina. We therefore prescribe one of the drugs that has the effect of dilating the coronary vessels. The most trustworthy of these are the *theobromine* and *theophylline compounds*. In our own clinic we use specifically alkaloidal theobromine, 5 grains four times a day, theocalcin, which is theobromine calcium salicylate,  $7\frac{1}{2}$  grains four times a day, aminophylline, which is theophylline with ethylenediamine, 3 grains three or four times daily. The latter may be given parenterally but this is rarely if ever necessary in the treatment of angina pectoris. Under certain conditions in which it is impossible to have medication retained in the stomach the intramuscular administration of aminophylline is indicated. Parenteral administration is usually limited to the treatment of coronary occlusion.



I feel that I should offer a few words about the theobromine and theophylline compounds, because there seems to be doubt in certain quarters concerning their efficacy. This is a question that the physician must answer from his own experience. Those of us who have done experimental work with these drugs cannot fail to be impressed by the effect on the coronary flow in the animal, and their efficacy in clinical usage seems equally plain to me. A high percentage of my own patients are greatly benefited by the proper administration of these drugs. It is true that one must again study the individual case. A routine handling is not satisfactory. Some patients will not tolerate one form of medication that may be given with impunity to another patient. I cannot see how careful administration of adequate doses of these purine base preparations will fail to benefit a large number of patients. It is, of course, obvious that in those patients whose vessels are rigid and sclerotic, dilatation by any means is almost impossible.

A striking testimonial to the efficacy of theobromine and theophylline is obtained when one attempts to persuade patients, particularly physicians, to get along without either drug after they have been rendered reasonably comfortable by its use. One obstacle to their use formerly lay in the gastric distress that accompanied their administration. This has been largely obviated by the newer preparations, and if the medication be given together with the meal, difficulty is seldom encountered.

Other drugs that are used for the dilatation of the coronaries are the *nitrites*, apart, of course, from those nitrites already mentioned. In my hands the effect has been too transient to be dependable. Furthermore, I believe the purine bases to be superior in effect.

The administration of a small dose of a *barbiturate* often seems to be effective in reducing the number or severity of anginal attacks, but I do not favor the combination of barbiturate and purine base in a single tablet. I prefer to be able to vary the dose of one or the other drug at will.

The parenteral administration of certain *tissue extracts* has been effective in some patients. This material is surely worth a trial if difficulty is encountered in controlling attacks by other means. In some cases, indeed, it seems to be superior to any other medication. Unfortunately its administration is time-consuming and this fact has had something to do with its less widespread

popularity When this material is used it must be given in adequate doses. This means a daily injection for a time, with a longer time interval later as indicated The patient may be taught to give his own injection but this always seems to me to be throwing too much responsibility upon the patient

The administration of *male sex hormone* (androgen) has been recommended Androgen has not been particularly efficacious in the relatively few cases in which I have used it Perhaps I have not been sufficiently persistent because in a few of my cases the results have been rather striking

*Drugs That Should Not Be Used*—There are a few contraindications in the use of drugs that probably should be mentioned Any drug that increases cardiac work should be avoided or given with great care The most common of these are *thyroid*, *epinephrine*, *ephedrine* and *benzedrine* As you may know, *digitalis* is one of my pet abominations I am already on record with my belief that digitalis may sometimes produce anginal pain To my mind the only indication for digitalis, apart from auricular fibrillation, is congestive heart failure, and congestive heart failure and angina pectoris seldom coexist I cannot see how digitalis can be of any benefit in angina pectoris and I feel sure that it may at times be harmful

### Surgical Measures

Some years ago *cervical sympathectomy* or *injection of the nerve trunks* was practiced as a means of interfering with the pain. Either may be justified in certain instances but is not recommended for widespread adoption Likewise, *thyroidectomy* has been effective in controlling anginal attacks but the cases must be selected with great care and this surgical procedure is not to be considered as a general routine treatment of angina pectoris

The surgical operations pioneered by Beck and O'Shaughnessy have been interrupted for the present. Perhaps this work will be resumed later and result in a means of creating an auxiliary coronary flow

### PROGNOSIS

I know of no situation in which it is more difficult to make an accurate prognosis The patient may die in his next attack and he may live for years Because of this uncertainty it is well that some member of his family be told of the possibilities. As a

general rule, it is unwise to tell the patient all of the possibilities, since few of us are able to face immediate extinction with mental tranquillity.

To those of you who may suffer from this disease, let me say that you travel in distinguished company. Some of the most famous men of history have suffered from the disease and even died from it

## HYPERTENSION

CHAUNCEY C. MAHER, M.D.\*

### DEVELOPMENT OF OUR KNOWLEDGE OF HYPERTENSION

By definition hypertension, or hypertensive vascular disease, is a syndrome in which there is persistent elevation of the blood pressure and left ventricular enlargement. Nephritis may or may not be a factor and it is generally accepted that complications are varied and frequent.

The term hypertension is a modern concept, as recent as the blood pressure instrument, which was introduced into the United States in 1902 by Harvey Cushing. The disease entity is of course much older, possibly as old as man. As a medical concept it probably began with recognition of cardiac enlargement. Lancisi was one of the first to recognize increase in heart size as an abnormality in his search for the causes of sudden death in Rome in 1709. He later wrote a book "Cardiac Aneurism" which was the terminology of cardiac hypertrophy of that day. There is little doubt that some of his cases are the same disease as those we now classify as hypertensive vascular disease complicated with acute coronary thrombosis.

About a century later, Richard Bright brought the subject of albuminuria before the profession, showing a relationship between chronic renal disease, cardiac hypertrophy, and apoplexy. The emphasis of the era was concerned with the renal aspect of the problem and therapy was directed toward kidney disease. Later it was determined that albuminuria was not always manifest early in the course of the disease, and sometimes was a very minor factor. Information accrued on arterial disease, and arteriosclerosis became part of the clinical concept.

With the advent of the blood pressure instrument in the present century, our modern view has emphasized the hyper-

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\* Associate Professor of Medicine, Northwestern University Medical School. Attending Physician and Chairman of the Department of Medicine, Cook County Hospital.

tensive state, with treatment directed toward blood pressure reduction

These three phases of the development of knowledge of this disease do not include a tremendous amount of research on many finer points which have amplified and extended the profession's information. Refinements of urinalyses, renal function tests and blood chemistry determinations have contributed to the study of the role of the kidneys in the problem. The x-ray and the science of fluoroscopy have augmented the knowledge of the changes in the shape and size of the heart and aorta. The electrocardiographic method has been an aid in the study of the complication of coronary thrombosis, and also in the study of left ventricular hypertrophy in the shift of the electrical axis. Ophthalmoscopic examination of the retinal arteries has given direct pictures of the vascular status.

#### PATHOGENESIS

With widespread use of the blood pressure instrument, it has been recognized that hypertension is associated with a number of disease entities. Chronic lead poisoning, formerly more common than now, is often linked with increased blood pressure and vascular disease. Other diseases recorded are less common, such as Paget's disease of the bone, coarctation of the aorta and congenital cystic kidneys. Chromaffin tumors of the adrenals have been proved by surgical removal to be the cause of paroxysmal hypertension. Others include periarteritis nodosa, brain lesions with increased intracranial pressure, polycythemia vera, arteriovenous aneurysm, hypothyroidism, and heart block.

Malignant nephrosclerosis has been separated as a distinct clinical entity, with exceptionally high blood pressures, a short progressive fatal course, and widespread arterial involvement particularly evident in the kidneys.

The role of syphilis in hypertension has also been of considerable interest. In the United States it has been conceded generally that the two diseases are unrelated, while in France, syphilitic hypertension has been recognized as a specific entity.

Experimentally, in the animal laboratory there have been repeated efforts to produce an artificial hypertension by surgical removal of kidney tissue, injury to the kidneys by chemicals or x-rays, or by production of multiple renal emboli. While some of these methods were somewhat successful they received com-

paratively little attention until Goldblatt achieved a method of partial clamping of the renal arteries and a satisfactory and practical procedure for consistent production of a hypertensive animal. The repetition of these operative procedures by decreasing the renal arterial blood supply has re-emphasized the renal aspect of the problem, with particular regard to the blood supply.

Within the last decade, the hypertensive vascular syndrome has been linked with chronic pyelitis and pyelonephritis. Our own studies along this line have suggested that the relationship included many urologic entities, indicating that the factor of obstruction in the urinary tract was a potent etiologic agent, as well as infection. We have noted frequently the association of hypertension with prostatism, renal stones, hydronephrosis, bladder diverticula, and have shown statistically that hypertension was more common in the urologic type of patient than in a control group of similar ages without urinary tract disease.

#### EFFORTS AT CLASSIFICATION

For many years it has been common practice to classify hypertension into two groups—the nephritic, representing about 5 per cent of the total, and the non-nephritic, the remaining 95 per cent. This latter group was labeled as *essential hypertension*, implying the absence of a causative factor, particularly a renal background. Actually, however, in clinical practice the label of essential hypertension was too often given without diligent investigation of all the clinical aspects of the individual case. Many of the aforementioned disease entities were not excluded. More recently, there has been an obvious trend toward classification of hypertension into a greater number of groups, and a gradual insistence that all cases demand more detailed study than in the past, abrogating the term essential hypertension. Most practitioners have been impressed that hypertensive patients have certain subjective symptoms and objective findings in common, and also with the fact that paradoxically there are divergencies that appear to separate individual cases. Complications often mar the true pattern of any individual patient.

#### Illustrative Cases

It is only possible to offer a few examples in this paper, illustrative of the similarity as well as the variability of the clinical pictures of hypertensive vascular disease. The following records

are offered in a chronologic sequence of medical events, as it has been our experience that the clinical pictures are best portrayed by this method of presentation

### Case I

(Observed from 1937 to 1942)

1882—Mr M E V, a lawyer, married, was born in a rural community His father died of apoplexy at the age of 74, and his mother of bowel obstruction at 62 A sister died of tuberculosis, and another of pneumonia

1896—Age 14, he had "bilious fever"

1900—Age 18, mumps was followed by atrophy of one testicle

1904—Age 22, measles

1914—Age 32, he was married

1928—Age 46, renal colic and hematuria occurred His blood pressure was said to be normal at this time

1930—Age 48, herpes zoster and mild arthritis were noted General examination in a university clinic recorded blood pressure as normal

1937—Age 55, re-examination in a university clinic revealed slight albuminuria and slight elevation of blood pressure Cardiac irregularity was noted (ventricular extrasystoles)

Routine examination later this year showed a negative record of subjective symptoms except for apprehension regarding the blood pressure elevation and the albuminuria The blood pressure level was 180/120 and a systolic murmur was noted at the heart apex The electrocardiogram showed a left axis deviation, the roentgenogram, an enlarged left ventricle, prominent aortic knob, and a substernal thyroid enlargement. The basal metabolic rate was normal, renal function tests were normal, blood counts normal, and the Wassermann reaction was negative.

1938—Age 56, an uneventful year with no subjective symptoms and no significant changes in the objective findings Blood pressure was 190/114

1939—Age 57, course continued without significant change Examination by a urologist showed "mild prostatic hypertrophy and slight residual bladder urine" Pyelograms were considered normal

1940—Age 58, no significant alteration of course noted Blood pressure 180/110

1941—Age 59, the course was uneventful during the early part of the year A routine examination, however, disclosed the presence of a systolic-diastolic murmur at the base of the

heart and change in blood pressure to 150/80. The cardiac roentgenogram showed no change in size and the electrocardiogram was unaltered.

In October, while on a vacation, in a mountain resort, the patient suffered a transient attack of nocturnal dyspnea with no pain. He subsequently noted dyspnea with exertion, and fatigue. On returning home a few weeks later, he was found to present evidence of cardiac insufficiency and was hospitalized. The electrocardiogram showed significant changes with coronary type of T waves in Leads I and IV. Compensation was readily regained with bed rest and fluid balance maintained after leaving the hospital.

1942—Age 60, this year was one of steady decline. The patient was unable to accept complete invalidism and alternated between a state of mild cardiac failure with activity and compensation when he was at bed rest.

In September, the final period of hospitalization was effected, and death occurred in November. During this last episode, the patient showed increased fluid retention in the lung bases, the liver, and lastly in the lower extremities. The blood pressure ranged around 150/70 with the persistence of the systolic diastolic basal murmur. In the latter part of the course the blood pressure fell to the lower levels of 100/60. Evidence of renal failure developed with increased amounts of albumin in the urine, a decrease of total blood protein, increased nitrogen levels in the blood, dyspepsia, anemia and mental confusion. The final episode of the course was concerned with severe chest pain, repeated hemoptysis, cyanosis, and air hunger, with increased edema throughout the body and finally death. The clinical picture was that of marked cardiac insufficiency, renal failure, mental confusion and malnutrition.

### *Autopsy Record*

The heart weighed 670 gm., with an incompetent aortic valve measuring 10 cm. The mitral valve showed fibrous thickening. There was one large old infarct in the left ventricle with a mural thrombosis and multiple small old infarcts.

The pleural cavities both contained fluid (700 cc. left and 150 cc. right). Both lungs showed pulmonary thrombi and infarcts. There was marked pulmonary arteriosclerosis. There was chronic passive congestion of the parenchymatous viscera, and recent thrombosis of both axillary and lateral thoracic veins.

The kidneys were labeled "arteriosclerotic and contracted" with a cortical cyst in the left kidney. The middle lobe of the prostate was markedly enlarged with mild enlargement of the lateral lobes. The bladder musculature was hypertrophied with marked trabecu-



lation of the wall There was a substernal cystademonia of the thyroid, hypertrophic arthritis of the spine, and generalized arterio sclerosis

## Case II

(Observed 1936 to 1943)

- 1899—Miss M F, single, clerk, was born in Chicago Her father died of pneumonia at age 67, and her mother of heart trouble at 73 One sister died of tuberculosis at 22 Four sisters and one brother living, have no knowledge of hypertension
- 1910—Age 11, she had "scarlatina" with no known complications
- 1911—Age 12, onset of menstruation "Swollen neck glands" were noted this same year
- 1917—Age 18, tonsils and adenoids removed
- 1922—Age 23, appendectomy.
- 1932—Age 33, gastro-intestinal study was made with diagnosis of spastic colon This same year she had a laparotomy and one ovary was removed Digestive symptoms were increased
- 1933—Age 34, in December, the patient was held up and robbed, and had a "mild nervous breakdown" She was told her blood pressure was elevated
- 1934—Age 35, she was hospitalized for "nervous exhaustion" Blood pressure again recorded as elevated.
- 1935—Age 36, hospitalization was accomplished for treatment of "spastic colon" Also, she was told she had migraine headaches
- 1936—Age 37, subjective complaints were nervousness, fatigue palpitation, dyspnea, frequency of urination, distention of abdomen, nausea and constipation Objectively, the patient was mildly obese with a blood pressure of 260/160, which was first recorded There was a systolic murmur at the apex and base of the heart and no evidence of cardiac insufficiency The Wassermann test was negative, blood counts normal urine negative, renal function tests normal, blood nitrogen elements not elevated The electrocardiogram was essentially negative except for a mild left axis deviation The cardiac roentgenogram showed only mild left ventricular hypertrophy Intravenous urograms were negative
- 1937—Age 38, the patient volunteered for splanchnicectomy and was hospitalized for extensive study The blood pressure showed a moderate decrease during sleep and with barbiturates Roentgenograms of the gallbladder, stomach and bowel were negative Gynecologic and urologic examinations were reported negative Ophthalmoscopic examination showed only

mild changes Renal function tests and blood chemistry findings were all normal The operative procedure was performed in two stages without incident except for acute pleuritis during the convalescence The preoperative blood pressure ranged around 250/140 Immediate postoperative level was 120/100, and on leaving the hospital 200/120

1938—Age 39, the patient was hospitalized for study Her subjective complaints were essentially unchanged and the objective findings were unaltered The blood pressure was 218/134 The urinalysis, blood counts, blood chemistry were within normal limits The electrocardiogram and cardiac roentgenogram showed no significant alterations Thiocyanate therapy did not change her subjective symptoms or lower the blood pressure levels

1939—Age 40, course unchanged She was hospitalized for a short period of time and the blood pressure was recorded as high as 270/170

1940—Age 41, the subjective and objective findings remained approximately the same, blood pressure record was 260/164 During the latter part of the year, she began to complain of cardiac pain with reference to the left arm The electrocardiogram showed increased width of the QRS complexes up to 0.12 second, with more marked inversion of the QRS in Lead III

1941—Age 42, the course was marked by frequent attacks of cardiac pain referred to the left arm and dyspnea became a more prominent symptom She collapsed while at work and was suspected of having an acute coronary thrombosis. Electrocardiogram showed progression of the width of the QRS complexes and the typical pattern of left bundle branch block There was no evidence of renal failure and cardiac compensation was maintained Blood pressure was recorded at 260/160

1942—Age 43, there was marked exaggeration of all symptoms and development of cardiac insufficiency Cardiac pain and dyspnea were even more frequent. The patient developed a tachycardia, gallop rhythm, enlarged liver and dependent edema The blood pressure was 220/140

1943—Age 44 further adverse progression of symptoms and findings was noted The patient became decompensated and bedridden, with leg edema and fluid in the lung bases With hospitalization, sedation, complete bed rest, and diuretic management she showed some recession of symptoms with a weight loss of 20 pounds of edema fluid Her course up to

the present date has remained approximately the same with moderate cardiac failure with edema. The blood pressure level has remained consistently high, around 240/130. She is still living

### Case III

(Observed from 1933 to 1937)

- 1871—Mr O J M, executive, married, was born in Chicago His father died of appendicitis at 37, his mother of heart disease at 76, and two brothers and one sister of heart disease Two sisters are living
- 1881—Age 10, he had the usual contagions of childhood prior to this age with no complications
- 1889—Age 18, a pulmonary hemorrhage occurred, diagnosed as pulmonary tuberculosis
- 1906—Age 35, he was married There were no children
- 1916—Age 45, minor attacks of "bronchitis" and rather frequent colds" occurred
- 1926—Age 55, he attributed frequent "bronchial colds" and chronic cough to tobacco smoking
- 1933—Age 62, the patient developed an acute lobar pneumonia and was hospitalized for oxygen therapy Shortly after entrance to the hospital an auricular fibrillation developed which terminated spontaneously within 24 hours During the convalescent period he developed an interlobar pleural effusion which was aspirated showing clear fluid The remainder of his convalescence was normal The blood pressure ranged around 150/90 during his hospital stay The blood Wassermann reaction was negative The first electrocardiogram showed the auricular fibrillation, and a second tracing was normal The roentgenogram during convalescence showed a mild prominence of the aortic knob and slight increase in markings in the right lung base Blood counts were normal except for the leukocytosis on entrance
- 1934—Age 63, a mild dysentery attack lasted about 10 days Stools were negative for amebas, and colon roentgenograms were normal Urine was negative Blood pressure was 200/100
- 1935—Age 64, during this year he developed a mild angina of effort Response to nitroglycerin was always prompt and he continued at work uneventfully The blood pressure remained around 190/90
- 1936—Age 65, the attacks of angina persisted and were present on less exertion The blood pressure remained elevated at 200/100 The electrocardiograms showed no change in pattern

1937—Age 66, the anginal attacks became much more frequent and the character of the pain was much more severe and lasting. The response to nitroglycerin became less prompt and the dose was increased from  $\frac{1}{150}$  grain to  $\frac{1}{100}$  and finally to  $\frac{1}{60}$ . The marked increase in the anginal syndrome strongly suggested an oncoming occlusion, which occurred in December.

The patient developed severe protracted pain in the chest radiating down both arms. Morphine ( $\frac{1}{4}$  grain) had no effect and a second dose was still ineffective in controlling the pain. The blood pressure was 176/128 on admittance to the hospital. Oxygen therapy relieved his pain and anxiety materially. The electrocardiogram showed a right bundle branch block, the leukocyte count rose to 13,500, and the urine showed albumin and casts.

The patient lived 4 days after admittance. His blood pressure gradually fell from the initial systolic level to 176 and down to 90 on the last day of life. The chest was filled with moist coarse rales. The patient became stuporous and died suddenly.

### *Autopsy*

The heart showed a left ventricular enlargement, weighing 560 gm, with extreme sclerosis of the aorta and coronary arteries. Thrombi were located in both the left and right main coronary arteries with extensive infarction of the left ventricle and the septum. Pericarditis (fibrinous) was also noted.

Both pleural cavities were obliterated by fibrous adhesions with marked scarring of both apices of the lungs. Bronchiectasis of the right lower lung was noted.

Other findings were cholelithiasis, diverticulosis of the colon, and varicose veins of the bladder.

### Case IV

(Observed from 1933 to 1943)

1870—Mrs. M. E., housewife, married, was born in Iowa. Her father died at 35 of an accident and her mother lived to the age of 88 to succumb to pneumonia. Her only sister had hypertension and apoplexy, dying at age 72.

1880—Age 10, she had measles, chickenpox and scarlet fever prior to this date.

1881—Age 11, onset of menstruation.

1889—Age 28, married (never pregnant).

- 1903—Age 33, appendectomy
- 1915—Age 45, fracture of the left ankle
- 1921—Age 51, routine examination because of indigestive syndrome revealed blood pressure of 135/85, negative urine and Wassermann reaction Roentgenograms of the stomach and colon were negative Achylia gastrica was found
- 1922—Age 52, menopause
- 1924—Age 54, removal of cervical polyp
- 1932—Age 62, she had a laparotomy for pelvic disease (operative procedure unknown)
- 1933—Age 63, mild angina of effort, fatigue, nervousness and distention of the abdomen were noted The blood pressure was 180/80, with a systolic apical murmur, and no evidence of cardiac failure The basal metabolic rate was plus 10 per cent, urine negative, Wassermann reaction negative, and blood counts normal The electrocardiogram was normal
- 1934—Age 63, her course was uneventful Blood pressure ranged from 140/80 to 210/90 She had one attack of "cystitis"
- 1935—Age 64, indigestive syndrome recurred with reappearance of angina of effort Graham-Cole roentgenogram of the gall-bladder showed stones Duodenal diverticula also were noted Blood pressure was 176/84 Electrocardiogram was unchanged Urine was negative
- 1936—Age 65, cholecystectomy was performed with uneventful recovery and marked improvement in gastro-intestinal symptoms and angina Blood pressure was 170/82
- 1937—Age 66, anemia was noted Gastric analysis showed no free acid The patient promptly responded to liver therapy Blood pressure was 190/90 A small postoperative hernia developed which was surgically repaired
- 1938—Age 67, course was unchanged Blood pressure was 200/100 Unexplained edema of the ankles developed Urine was negative Electrocardiogram was unchanged
- 1939—Age 68, blood pressure was 180/90 She was emotionally upset over her sister's apoplexy and death She had an unclassified dermatitis
- 1940—Age 69, her course was uneventful Blood pressure was 160/90
- 1941—Age 70, intermittent claudication developed The oscillometric readings on the left leg were zero Blood pressure was 180/90 During this year the patient had a mild cerebral thrombosis with apparently complete recovery
- 1942—Age 71, in February, the patient had an acute influenzal bronchitis lasting about a week Following this an arthritis of the

hands occurred, later involving the ankles and shoulders. Roentgenographic studies showed both hypertrophic and atrophic bone and joint changes. Blood pressure was 200/90.

1943—Age 72, the arthritis problem was persistent and gastro-intestinal symptoms became evident including anorexia, weight loss, mild nausea and distention. Roentgenographic examination of the stomach showed a carcinoma and later the tumor mass was palpable. Bone roentgenograms were negative for metastases. The weight loss continued although the blood pressure remained elevated around 180/80. The patient is still living.

### Case V

(Observed from 1935 to 1937)

- 1878—Mrs. R. M., widow, housewife, was born in Chicago. Her father died at age 78 of pneumonia and her mother at 76 of influenza. One sister and one brother died of pneumonia.
- 1884—Age 6, measles
- 1897—Age 19, married
- 1898—Age 20, first pregnancy with no complications
- 1900—Age 22, second pregnancy with no complications
- 1902—Age 23, third pregnancy with no complications
- 1904—Age 25, fourth pregnancy with no complications
- 1905—Age 26, fifth pregnancy, stillbirth
- 1909—Age 30, sixth pregnancy, "blue baby"
- 1911—Age 32, seventh pregnancy with miscarriage at 4 months
- 1912—Age 33, eighth pregnancy, stillbirth
- 1913—Age 34, ninth pregnancy, miscarriage at 6 months followed by postpartum hemorrhage and then sepsis. She was hospitalized for 5 weeks and was said to be in "delicate health" following this pregnancy.
- 1923—Age 44, she was operated on for "inward goiter." Following this she was in a sanitarium for 6 weeks.
- 1925—Age 45, she was in a sanatorium for an illness classified as "sunstroke." Blood pressure was said to be 150 systolic.
- 1933—Age 53, a diagnosis of "albuminuric retinitis" was made. She was also told she had high blood pressure.
- 1934—Age 54, she had apoplexy followed by weakness of the right arm and leg. She also lost the sight of her right eye this year, said to be due to a hemorrhage into the retina.
- 1935—Age 55, vision in the left eye was lost. Subjective symptoms at this time were fatigue, poor vision, headaches, weakness of right arm and leg, nosebleed, and frequency of urination. Her blood pressure was 280/160. There was a systolic murmur at the apex and base of the heart. Ophthalmoscopic ex-

amination showed "bilateral optic atrophy with closure of both central retinal arteries" The blood counts showed a moderate anemia, the urine showed 2 plus albumin and a few casts The Wassermann reaction was negative The blood urea nitrogen was 22.2 mg The phenolsulfonphthalein test showed an excretion of 35 per cent and concentration of urine 1 012 with dilution to 1 001 The basal metabolic rate was minus 12 per cent The electrocardiogram showed a normal axis deviation with coronary defects in the T waves of Leads II and III The heart showed a marked left ventricular hypertrophy and a prominent aortic knob on the roentgenogram

1936—Age 56, urologic examination revealed a diverticulum of the bladder, stricture of the urethra, a functionless right kidney and a small contracted left kidney The blood pressure ranged around 260/150

1937—Age 57, progressively adverse course followed Her symptoms of fatigue, dyspnea and headaches became worse and edema gradually became evident She entered the hospital a few weeks prior to death in a state of marked cardiac insufficiency with edema, evidence of renal failure (blood urea nitrogen 71.4 and creatinine 4.70), and marked anemia She lapsed into stupor and coma

### Autopsy

The heart weighed 540 gm, with marked sclerosis of both coronary arteries, and the thoracic and abdominal aorta The splenic artery showed unusual calcification

The right kidney was a lobulated hydronephrotic sac filled with cloudy fluid, with a hydro-ureter extending to the diverticulum of the bladder The right kidney was small with a thickened capsule, a sclerotic renal artery, and was classified as "nephrosclerotic" histologically

Incidental findings were old ulcer scars of the stomach, a recent superficial gastric ulcer, a small cyst of the liver, and passive congestion of the abdominal viscera

### COMMENT

The case records which have been presented are characteristic examples of the common, and some of the rarer, problems presented by patients with hypertensive vascular disease They show *persistent* elevation of blood pressure, and left ventricular enlargement is a common denominator to all Vascular disease is also a pertinent part of each individual record

Another common factor is the insidious onset, unmarked by any particular clinical episode. The course of each was measured in years, with a slow but inevitable evolution

*Case I* is a typical record in most respects, but exceptional with regard to the development of a relative aortic regurgitation. Hypertension is a common problem in the professional group, of which this lawyer was a common example. This particular patient was identified in his legal activity with a life insurance company and was well informed in life insurance statistics regarding blood pressure and albuminuria. While his course was practically symptom-free until the latter part, he was apprehensive and pessimistic about his future. When he developed the functional valvular incompetence, it apparently did not embarrass him until the further complication of coronary involvement was added. The coronary occlusion was exceptional because of the absence of pain and the dramatic collapse usually attending vascular thrombosis.

The terminal process was of interest because of the combination of both cardiac and renal failure. The final fall in blood pressure was coincidental with the development of the uremia, although the two processes may have been unrelated. The obstructive aspect of the midlobe of the prostate with the thickened bladder wall and the trabeculated bladder lining suggest that obstruction may have been a factor in the renal failure, although clinically no subjective symptoms suggested this possibility.

Another point was the multiplicity of the vascular pathologic processes—generalized arteriosclerosis, coronary sclerosis and thrombosis combined with pulmonary arteriosclerosis and thrombosis and terminally venous thrombi. The clinical and pathological record substantiates the older conventional terminology of cardiovascular-renal disease.

*Case II* represents the occurrence of hypertension at a much earlier decade of life, with a less complicated clinical picture. Subjectively, however, this patient presented a much greater intensity of symptoms almost from the beginning of her course and much greater hypertensive level. She has seemed remarkable in regard to the tenacity with which she has been able to carry on despite the height of the blood pressure, both systolic and diastolic, for so long a period of time.

Another interesting note is the negative result of the splanchnicectomy. The blood pressure fell to an extremely low level.



following the surgical procedure, but soon resumed the preoperative level and the result must be tabulated as completely negative. Her response to thiocyanate therapy was equally negative, either as to relief of subjective symptoms or objective results.

Presumptively this patient should have advanced coronary disease in view of the persistent cardiac pain, the distortion of the electrocardiographic pattern and the advent of myocardial failure. Her blood pressure level, however, has not been lowered to any great extent with this complicating factor. The renal aspects seem to have been a minor part of her clinical picture, and the vascular pathology clinically appears to be limited to the coronary circuit.

*Case III* shows a number of points of interest, particularly the dramatic coronary episode which terminated the clinical course so promptly. It is worthy of note that this patient began life with tuberculosis, and respiratory disease marked his whole life. It should also be remarked that the first cardiac episode was a transient auricular fibrillation which developed during the stress of the lobar pneumonia.

This patient was of unusual interest in the stage prior to his occlusion, as his angina gradually grew in intensity, in frequency, and the response to nitroglycerin diminished. It was obvious that acute coronary thrombosis was imminent, and equally obvious that prevention was impossible. Prompt hospitalization, oxygen therapy and sedation did not prevent a fatal outcome of the coronary occlusion.

*Case IV* is variant with regard to the termination by cancer of the stomach after a long record of hypertension and advanced vascular disease. The vascular involvement was clinically manifest first with angina and presumptively coronary sclerosis without evidence, however, of any occlusive phenomenon. The record then points to the peripheral arteries, with intermittent claudication, probably complete occlusion, and the development of a collateral circulation. Laterally, a disturbance of the cerebral circuit became manifest and the terminal phase of the patient's course has been distorted by seemingly unrelated medical entities—arthritis and carcinoma of the stomach.

The degree of arterial vascular involvement apparently has been severe as well as widespread, but the local lesions (coronary, peripheral, or cerebral) were not lethal and the patient

has been able to live out a normal life span, contrary to statistical averages

*Case V* is of significant interest in many respects. The record suggests that the hydronephrotic kidney had its inception in the puerperal sepsis of the last pregnancy. If it is assumed to have existed for some years, the patient apparently lived with a greatly decreased functioning renal parenchyma and finally succumbed when the remaining kidney failed to function. It seems reasonable to believe that this record supports the contention that uropathic disease is a causative factor of hypertension as well as chronic glomerulonephritis. The vascular involvement was both clinically and pathologically severe, but not lethal. The thyrotoxicosis, assuming the diagnosis was valid, apparently was unrelated to the hypertensive process.

### CONCLUSIONS

The presentation of these five clinical records suggests the fundamental inadequacy of our knowledge of hypertensive vascular disease. The clinical records may be documented from month to month or year by year, as cardiac, vascular, or renal episodes are diagnosed with reasonable certainty or even predicted in advance on some occasions. Therapy may minimize subjective symptoms but the course of the disease seems unalterable and up to date no one has visualized the basic causative principle involved in this disease.

One may aptly compare the present state of our knowledge of hypertension with the concept of physicians of former years of "continued fevers." There was an era when fever was looked upon as a single disease entity, and therapy was directed toward decreasing the hyperpyrexia. Today a fever that cannot be classified as typhoid, miliary tuberculosis, subacute bacterial endocarditis or another well defined disease constitutes a challenge to the hospital resident and attending staff. Hypertensive vascular disease in all probability represents a number of specific disease processes in which the hypertension is a cardinal feature but less important than it is now generally esteemed. Therapy throughout two centuries has obviously been inadequate and our modern attempts seem of no greater effectiveness than those of our predecessors.

Experimentally, relatively little has been accomplished. One method (partial ligation of the renal arteries) has been success-

ful in producing an artificially sustained elevation of blood in animals. There have been a few well documented clinical and pathological records which are counterparts of this experimental method. The premature suggestion that this method is an adequate explanation of the so-called essential hypertension seems quite unwarranted.

Clinically, cardiac and renal failure are recognized with reasonable accuracy and localized vascular lesions of the brain, heart or extremities are usually well defined. Although the diagnostic accuracy of the profession has been increased, it would not appear that any real progress has been made to specify the underlying cause or causes of the disease process.

The future will undoubtedly reveal much to us regarding the mysteries of this problem, although there are many practical difficulties to obstruct productive research. This disease or group of diseases is one in which the course is measured in years, as a rule, and seldom does any one physician have a complete clinical document of an individual patient. The medical records are more often widely distributed in a number of physicians' files or hospitals and the final episode presented to a pathologist for evaluation represents only a minor portion of the complete history. A better correlation of records by the clinician, and particularly those in specialties for postmortem analysis, may prove of some help.

The final answer, however, is more likely to be found in some entirely new line of thought, as revolutionary as the discovery of bacteria or the solution of the deficiency diseases.

## MITRAL STENOSIS

DON C SUTTON MD\*

MITRAL stenosis is almost always the result of a benign endocarditis induced by acute rheumatic fever. It has been described as a congenital lesion, but in all the cases reported the lesion is either a complete atresia or so nearly so as to be incompatible with life. It appears possible that there may be an extremely rare congenital stenosis of the valve that is compatible with life. Mitral stenosis may also in rare instances be the result of atherosclerotic changes in the valve leaflets.

The inflammation of the valve which occurs in rheumatic fever is a nonulcerative lesion and therefore does not cause formation of thrombi. Embolic phenomena are absent. The valve changes are found principally on the edges of the cusps which are thickened and often adherent to one another. With the healing process the valves, particularly the edges, are thickened and as the scars contract become distorted and irregular. The adhesions become firm and further distort the valve. The chordae tendineae are often involved with thickening and loss of elasticity. The end result is narrowing of the mitral orifice to a varying degree and almost invariably there is enough irregularity of the valve edges to prevent complete closure, resulting in a concomitant valvular insufficiency.

Mitral stenosis diminishes the amount of blood expelled during each systole and results first in dilatation of the left auricle and stasis in the pulmonary venous bed, and ultimately in an increase of pressure in the pulmonary artery with hypertrophy and dilatation of the right ventricle. The increased pulmonary venous pressure causes pulmonary edema and dilatation of the venules. Dilated pulmonary veins often rupture causing hemoptysis. Because of the decreased amount of blood flowing into the left ventricle the pulse is small and increased in rate.

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\* Associate Professor of Medicine, Northwestern University Medical School; Attending Physician, Cook County and Evanston Hospitals.

From a prognostic viewpoint the most important observation is the degree of stenosis present. Helpful signs in its evaluation are (1) a marked mitral facies, namely flushed cheeks, flushed, slightly cyanotic lips and ear lobes, (2) the smallness and rapidity of the pulse, and (3) a mid-diastolic murmur.

## COURSE AND PROGNOSIS

### Illustrative Cases

CASE I—MISS B, now forty-four years of age, had her first attack of rheumatic fever at the age of nine years. At this time her parents were told that she had an injured heart valve. Two years later she again had an attack of rheumatic fever followed by chorea which lasted several months. As far as she knows the heart was not further damaged by these attacks.

After this attack she continued well for years. She attended a private school and a woman's college. After finishing college she led a moderately active social life always restrained by a solicitous mother. Her father died when she was twenty-five years of age and since that time she and her mother have been constant companions. After her father's death she spent some time every year at one of the European spas although she enjoyed excellent health.

While in Europe the panic of 1929 occurred and she returned home to find her income greatly reduced. She was much upset and consulted me because of palpitation and breathlessness. She was found to have a moderately high grade mitral stenosis and insufficiency but was well compensated and required no medication. Her heart was moderately enlarged to both the right and left, i.e., a typical mitral-shaped heart. At the apex was heard the typical pre-systolic murmur, a systolic murmur and a very much accentuated pulmonic second sound.

Beginning in 1935 through 1938 the patient reported attacks of what were called gallbladder colic. These attacks always occurred during a trip out of town. In the latter part of 1938 she was given a routine examination which revealed no change of her status. Two hours later she was seen because of another attack of "gallbladder colic." These attacks were then explained. Her liver was acutely enlarged to a hand's breadth below the costal margin and was painfully pulsating.

Her so-called colic, then, had been temporary attacks of right heart failure with the development of a relative tricuspid insufficiency. During 1939 these attacks occurred with increasing frequency and finally by the end of the year the tricuspid insufficiency became permanent.

Early in 1940 a permanent auricular fibrillation developed, the ventricular rate of which has been easily controlled by the administration of digitalis. During the entire period of my observation of her she has complained frequently of joint pains, at times accompanied with a low grade fever which makes one wonder if she still harbors a mild infection of rheumatic fever.

Since 1940 her cardiac reserve has very gradually but definitely diminished. The apex now extends almost to the axillary line and the right border extends 4 cm to the right of the sternal line. There is now a definite mid-diastolic murmur which indicates a more advanced stenosis of the mitral valve. There are moist rales heard at the base of both lungs posteriorly. Also it is necessary to give her ammonium chloride and mercupurin at four- to six-week intervals to control the edema in spite of greatly decreased physical activity.

Recently, examination has revealed a very firm liver with less obvious pulsations, an enlarged spleen and a gradually increasing ascites. These changes in the liver and the onset of the ascites are due to progressive fibrosis in the liver following the prolonged passive congestion with a progressive obstruction of the portal vein.

This woman has run a course much better than the average in my experience. Economically, she has been able to lead a life that appears to be ideal for one with mitral stenosis. It is true that one occasionally sees such a patient who lives into the seventies, but in my statistics from the Cook County Hospital Cardiac Follow-up Clinic and my private practice the optimal duration of life in 95 per cent of cases of mitral stenosis is forty-five years for women and fifty years for men.

**CASE II**—This fifteen-year-old colored boy has been in my ward for the past five months. He entered the hospital because of a severe attack of acute rheumatic fever which lasted for three weeks. At ten years of age he had the first attack of rheumatic fever which left him with a mitral stenosis and insufficiency. When he first came into the ward he had a mitral stenosis of moderate degree and also a questionable insufficiency of the aortic valve. The latter lesion has become much more pronounced because of the infection which will be described.

When his convalescence from the rheumatic fever began he developed an abscess of a left lower molar, for which the tooth was extracted. Following the extraction he developed a septic type of temperature, with fever ranging as high as 103° F. This fever has continued to the present time. Repeated blood cultures have been negative, nevertheless we believe this to be a subacute bacterial

endocarditis He has had a moderate leukocytosis and a persistently high sedimentation rate

This case represents a not infrequent course, with repeated attacks of rheumatic fever ending ultimately in a frank bacterial endocarditis which ultimately will be fatal

CASE III—This young man, now twenty-four years of age, had his attack of rheumatic fever at twelve years of age from which he evidently developed a benign endocarditis of the mitral valve with mitral stenosis and insufficiency He was well until two weeks before entering the hospital three weeks ago, having spent the last five years doing moderately heavy work in a machine shop Five weeks ago he developed fever and red, painful, swollen joints

At the time of entrance he presented the findings typical of rheumatic fever The fever reached  $103^{\circ}$  to  $104^{\circ}$  F and was of the daily septic type Within a few days petechial spots were seen in the conjunctivae and in the soft palate The first blood culture revealed many colonies of a green-producing streptococcus

This case represents a frank bacterial endocarditis due to the organism most commonly found when bacterial endocarditis occurs as a complication in cases of old rheumatic valvular disease, namely the *Streptococcus viridans* This, unfortunately, is a frequent complication, occurring at any time after the initial valvular injury, so that bacterial endocarditis is seen in individuals ranging from ten to forty-five years of age Unfortunately on the whole this disease is always fatal In a large series we have records of six cases which recovered spontaneously There is an increasing number of reports of recovery following the use of the sulfonamide compounds but yet a pitifully small number in relation to the number of failures

CASE IV—This woman, aged forty years, has been a regular attendant in the Prenatal Division of the Cardiac Follow-up Clinic for the past twelve years When she was referred to the clinic she had a well developed mitral stenosis She is unable to give any history of an acute rheumatic fever, chorea or even frequent attacks of tonsillitis In fact, she was unaware of having any heart disease until she was referred to the Cardiac Clinic Nevertheless she had already borne five children and since she has been attending the Clinic has borne six more She still is well compensated although she has a more than moderate mitral stenosis

This woman is representative of a very large group of individuals having rheumatic heart disease who are or have been completely unaware of the condition until it is found as the result of a physical examination for another cause. For some reason these persons are unable to give a history that explains the onset of the valvular endocarditis, which may be due to a mild rheumatic infection that was overlooked or was later forgotten. Among 247 cases of mitral stenosis observed in the Prenatal Heart Clinic, only 32 per cent gave a history of rheumatic fever or chorea.

### Pregnancy and Mitral Disease

There is considerable controversy as to whether the woman with mitral disease should marry and if she does should she bear children. Of course there is no question as to the advice to be given a young woman who has a high grade mitral stenosis or for some other reason is barely able to maintain a compensation. On the other hand, there is a large group of both sexes who, following an attack of rheumatic fever, enjoy excellent health for many years, say until thirty-five to forty years of age. In this group it is our observation that it is safe for women to marry and bear children. Among our group of 247 cases in the Prenatal Cardiac Clinic not a single patient died during pregnancy or labor. One died six weeks postpartum of bacterial endocarditis. During the same period 60 per cent of the women entering the hospital without prenatal care and decompensated died. It is then evident that the pregnant woman with mitral stenosis requires special care, but with such care fares as well as her more healthy sisters.

It is also stated by some authorities that, although the woman with mitral stenosis may not die during pregnancy or labor, when such women bear children their life span is shortened thereby. From the general heart clinic we compiled a series of 118 patients who had no pregnancies, and one of seventy-nine patients with one or more pregnancies. Between the ages of twenty and thirty years, 10 per cent of both groups died. Between the ages of thirty and forty, 16 per cent of the nonpregnancy group died and only 10 per cent of the pregnancy group died. Between forty and fifty years, 27 per cent of the nonpregnancy group died whereas only 17.7 per cent of the pregnancy group died.



## Other Factors Affecting the Course and Prognosis

The course and prognosis of mitral stenosis are difficult to discuss in general terms as each individual case presents its own problems. Practically every case of mitral stenosis is combined with mitral insufficiency, however, the mitral stenosis is the lesion having the greatest mechanical effect upon the circulation. With increasing narrowing of the mitral orifice there is a progressive pulmonary congestion. This back pressure in the pulmonary veins leads to diminished aeration of the blood with cyanosis and dyspnea. Pulmonary vessels may rupture causing blood-stained sputum or even frank and at times fatal hemorrhage. Increased pulmonary vessel pressure increases the load upon the right ventricle, which may fail with resultant peripheral edema with or without a relative tricuspid insufficiency. These symptoms may be primarily the result only of the narrowing of the mitral orifice and their severity depends upon the smallness of the opening.

The effects of mitral stenosis within the limits of extreme narrowing are greatly influenced by the *degree of damage the myocardium has suffered* from the rheumatic infection. Every attack of rheumatic fever causes some damage to the heart muscle. If this is severe the heart may be unable to cope with even a mild stenosis, or if the damage is little then a severe stenosis may be tolerated for many years.

The course of mitral stenosis is further influenced by the *degree of injury to the pericardium* by the rheumatic infection. Besides changes in the endocardium and myocardium, inflammation of the pericardium is a not infrequent lesion. This lesion may vary from a slight fibrinous pericarditis to one involving the whole pericardial sac. This inflammation may further result in a pericarditis with effusion. If the patient recovers there is often left a varying number of adhesions between the visceral and parietal pericardium even to the extent of complete obliteration of the pericardial cavity. Moderate to extensive adhesions interfere severely with the mechanical efficiency of the heart.

*Exercise and work* exert an important influence upon both the course and prognosis of mitral stenosis. For many years we have limited the exercise and work of children and adults under twenty-five years of age only upon evidence of overexertion, as dyspnea or edema of the extremities. We have found that a

large number of young adults can continue strenuous sports as boxing, swimming, tennis, football and basketball without harm. We believe those individuals who can do strenuous exercise without adversely affecting their cardiac reserve are building an hypertrophy of the heart muscle that gives them a reserve to help compensate for the valve defect in later years. However, when one observes the effects of hard work over a period of years it is evident that strenuous work should be limited to those under possibly twenty-two years and certainly under twenty-five years of age.

When no other cause intervenes, most laborers who have mitral stenosis suffer their first decompensation at about thirty-five years of age. This is at least true for the type of patient we have in the Cook County Hospital. Those of more sedentary occupations carry on over a longer period.

The child with mitral disease should be trained in the lighter occupations and told to cease strenuous exercise between twenty and twenty-five years of age.

*Infections* varying from ordinary "colds" to the more severe ones are always likely to affect the myocardium adversely. Patients with even mild infections should be put to bed promptly and their convalescence prolonged until one is sure the heart has recovered completely from any adverse effects of infection. Acute infectious disease is also very likely to be the forerunner of an attack of acute rheumatic fever or even a bacterial endocarditis.

*Bacterial endocarditis* usually due to the *Streptococcus viridans* is always a potential complication of rheumatic heart disease and is a frequent cause of death in such cases.

The onset of a cardiac irregularity, especially an auricular fibrillation, may be the precipitating cause of failure in mitral stenosis. Repeated attacks of *paroxysmal tachycardia* of auricular origin often precede the onset of an auricular flutter or auricular fibrillation. Such attacks are usually of short duration but if prolonged for several hours may lead to decompensation.

*Auricular flutter* occurs most commonly in mitral stenosis and if not paroxysmal and of short duration leads to heart failure. *Auricular fibrillation* like flutter is usually a complication of mitral stenosis, this lesion being the cause in 70 to 80 per cent of the cases. Auricular fibrillation may occur in paroxysmal form lasting a few minutes to days. When it becomes a perma-

nent irregularity it almost always results in acute heart failure with the usual symptoms of dyspnea, cyanosis and edema. Without digitalis therapy, auricular fibrillation with mitral stenosis would almost invariably cause early death. The slowing of the ventricular rate by digitalis therapy leads usually to compensation and in many cases patients may continue in a relatively good state of health for a number of years. We have a number of such patients who have attended the clinic some ten to fifteen years, and during this time have been able to maintain themselves at work. In auricular fibrillation the auricles assume permanently the position of diastole. In such distended auricles mural thrombi frequently form, especially in the auricular appendages. Emboli breaking from these thrombi may be the cause of cerebral embolism, pulmonary embolism or emboli to the periphery, causing gangrene of an extremity or infarction of an organ as the kidney or spleen. At autopsy multiple, clinically unrecognized pulmonary emboli are often found.

#### SUMMARY

The prognosis of stenosis of the mitral valve depends upon

- 1 Age. Very few individuals live beyond the age of fifty years.

- 2 The degree of stenosis present. The smaller the mitral opening the greater the mechanical difficulty of the heart in maintaining an adequate circulation.

- 3 The amount of permanent damage to the heart muscle lessens the ability of the heart to compensate for the stenosis.

- 4 Adhesive pericarditis depending upon its extent greatly hinders the contractile power of the ventricles and interferes as well with the filling of the auricles.

- 5 The demands made upon the heart by work are extremely important in the maintenance of compensation. In youth, exercise within limits of tolerance may serve to build a heart muscle hypertrophy which furnishes a reserve for later life. Continued strenuous exercise or work leads to earlier failure than do more sedentary occupations.

- 6 Infectious diseases may interfere with compensation in mitral stenosis as the result of toxic injury to the heart muscle, as a precipitating cause of a recurrent rheumatic fever, or as the cause of a bacterial endocarditis. Bacterial endocarditis usually

due to the *Streptococcus viridans* is a frequent fatal complication of mitral stenosis.

7 A cardiac irregularity, such as paroxysmal tachycardia, auricular flutter or auricular fibrillation, may be the cause of acute heart failure. Paroxysmal tachycardia is the least frequent cause. Auricular flutter is the next most frequent and the most serious in its effects upon the circulation. Auricular flutter is the most frequent permanent irregularity in mitral stenosis.

## HEART BLOCK\*

ITALO F. VOLINI, M.D., F.A.C.P.†

THE extensive use of electrocardiography has greatly expanded the subject of heart block. In fact, by far the major number of diagnoses of heart block in the minor degrees of this disturbance of conduction is recognized by this mode of examination alone. Even what may be considered major and very serious types of heart block, such as bundle branch block, are often revealed only by the graphic registration. Recognition by clinical signs and symptoms particularly in the presence of a regular cardiac rate and rhythm is practically impossible. Associated evidence even when present is meager, equivocal, indecisive and requires the aid of electrocardiography to establish a definite diagnosis.

Heart block defined is an arrhythmia involving the conducting mechanism of the heart, with inability to transmit the impulses in a physiologic manner from the auricles to the ventricles. Auriculoventricular heart block implies an extensive range of disturbances varying from the simple increased functional activity of vagal tone producing a mild delay in impulse transmission to the total inability of the conducting system to pass on stimuli from the auricle. In the former the administration of atropine clears the delay completely, while in the latter the use of a long list of potent drugs usually effects no change.

### COMPLETE HEART BLOCK

While in certain rare cases of complete heart block, the ventricles may contract more rapidly than the auricles, the classical picture of complete heart block shows a very slowly acting ventricle. This common type, although not often encountered

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\* From the Cook County Hospital and the Department of Medicine, Loyola University School of Medicine.

† Professor of Internal Medicine and Chairman of Department of Medicine, Loyola University School of Medicine, Senior Attending Physician and Director of the Department of Medicine, Mercy Hospital—Loyola University Clinics.

in clinical practice, is frequent enough to be readily recognized because the clinical symptoms and manifestations present a clear-cut typical pattern

Thus, Mrs I K, a white woman aged sixty-two years, was admitted to the Volini Medical Service at Cook County Hospital on April 19, 1943, her third entrance in two years. She complained of dizzy spells which occur at anytime but more frequently on standing or exertion, rather than at rest. Syncopal attacks often follow the periods of vertigo. The patient does not know what happens to her while unconscious, although she describes her state at these times as paralyzed. The extremities jerk at times during the episodes of unconsciousness. Dyspnea is present only on effort. Nocturia two or three times a night is described. There was a history of palpitation two years ago, but this subsided with the onset of the present complaint. The complete history otherwise has no direct bearing on the present illness or on the presentation of this symptom complex which will be discussed from the clinical and laboratory evidence.

The *physical examination* has the following positive features which directly concern our subject of complete heart block. The general appearance of the patient is alert, not presenting an acute illness. She rests quietly on one pillow, not complaining very much. The pulse rate is 38 per minute. The apex rate with the stethoscope is 38. The blood pressure is 240 systolic and 80 diastolic. The eye grounds show tortuosity and silver streaking of the vessels with nicking, but no old or new exudate or hemorrhages. The heart is enlarged with the left border 12 cm. to the left of the midsternal line, physical evidence which is corroborated by the 2-meter chest film. The heart rate is slow, 38 per minute at the apex. The sounds are good, slow, strong and regular with a systolic murmur found at the apex with another systolic murmur which is louder over the aortic area and transmitted up into the neck vessels. Auricular activity can be visualized in the external jugular veins during the interventricular soundless period, but the evidence of sounds audible by use of the stethoscope produced by the contraction of the auricles cannot be detected. Auricular contraction can be seen by the fluoroscopic examination while the ventricles remain immobile. The clinical diagnosis is definitely indicated by

this classical pattern of complete heart block occurring in coronary arteriosclerotic heart disease

The *electrocardiogram* shows the auriculoventricular dissociation with a regular auricular rate of 75 per minute, while the rhythmic ventricular autonomic rate is 40. A somatic tremor distorts the graph especially the P (auricular) waves, but the neuromuscular distortion can be neutralized by viewing through the partially closed lids of the observer, which render the auricular waves clear, prominent and more evident. Left axis deviation and intraventricular conduction deformity are also noted in the complete graph (Fig. 1)

While no complaints were manifested while the patient was at rest in the ward, *vertigo* was present on slight activity. This demonstrated the well known fact that despite the slow ventricular activity, an adequate minute volume output is maintained approximately equal to the output during normal ven-



Fig 1—Complete heart block with auricular ventricular dissociation or idioventricular rhythm

tricular rates of 72 to 80, sufficing for metabolic demands at rest. This is accomplished because of the greater filling during diastole, the more complete ventricular emptying, with the high systolic pressure. During physical activity or because of other demands for increased output, the secondary autonomic center of impulse production for ventricular control becomes exhausted. Thus ventricular standstill occurs, which results in cerebral anemia and the Stokes-Adams syndrome appears. These episodes were very vividly indicated by the patient's story. These seizures were described as both apoplectic and epileptic.

Recovery ensued as a result, first, of resting of the secondary center for the idioventricular rhythm control, so that metabolic action could be resumed, and secondly, of irritating metabolites which produced contraction of the ventricles and thus improved the anoxemia, focally, locally and generally. This improvement results from oxygen and blood movement.

## Drug Therapy in Complete Heart Block

In unpublished studies made for the purpose of evaluating the effect of various drugs used to increase the ventricular rate in complete heart block of coronary arteriosclerotic disease origin, none was found effective. They included atropine, epinephrine, ephedrine, amphetamine, nitroglycerin, barium chloride, thyroid extract, metrazol, nikethamide and the xanthine group of compounds. The occasion did not arise in the present case for the intracardiac injection of epinephrine. The patient had no attacks of ventricular asystole causing Stokes-Adams seizures during her stay in the hospital. While complete heart block may rarely be temporary, as when induced by digitalis and rheumatic fever, auriculoventricular dissociation is much more of an organic permanent variety. A few weeks to several months waiting time distinguishes and cures the temporary form.

After determining the ineffectiveness of these drugs to improve the ventricular rate, vagal stimulation by carotid sinus pressure was attempted to see if further slowing would occur. The action was negative. However, ventricular standstill was induced by the subcutaneous injection of 10 mg of mechohyl, the cholinergic parasympathetic stimulant. The action was immediate. Fortunately, atropine sulfate injection restored the ventricular activity before intracardiac injection of epinephrine was necessary. Digitalis does not aggravate an idioventricular rhythm and can be and should be prescribed when indicated in complete heart block. While complete heart block may rarely be temporary, as when induced by digitalis and rheumatic fever, auriculoventricular dissociation is much more commonly encountered on a permanent basis from a vascular origin. This results from the closure of the blood supply of the auriculoventricular node and the auriculoventricular bundle which receives blood almost entirely from one special branch of the posterior descending division of the right coronary artery. Occasionally, calcification of the interventricular septum at the site of the auriculoventricular bundle is also present.

In very rapid supraventricular stimuli such as occur in auricular fibrillation, auricular flutter and extremely rapid auricular paroxysmal tachycardia, auriculoventricular heart block is, in reality, a physiological mechanism. Under these conditions, stimuli are received at the auriculoventricular node faster than



the node or bundle can normally function as a conducting system Only those stimuli which this upper physiological limit can accept, pass through, and are thus transmitted along the conducting system The ventricles then respond This upper limit is approximately 190 The grade of block can be readily recognized as a rule by the electrocardiographic tracing

#### FIRST DEGREE HEART BLOCK (DELAYED CONDUCTION TIME)

The simplest type of heart block is recognized by graphic means alone The commonest causes are digitalis, rheumatic fever, and arteriosclerotic coronary disease (Fig 2), although

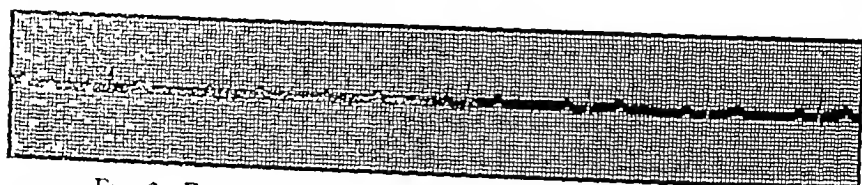


Fig 2—First degree heart block in coronary arteriosclerosis

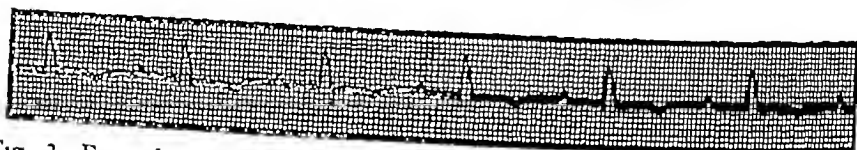


Fig 3—First degree heart block seen in Roger's disease No digitalis was used A large interventricular septum defect was found postmortem

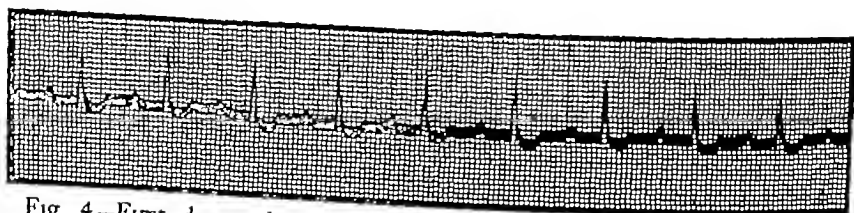


Fig 4—First degree heart block The P-R interval is prolonged to 0.28 seconds and is the result of the action of digitalis The digitalis effect is noted on the S-T segment.

it may result from congenital heart lesion (Roger's disease, Fig 3), asphyxia, diphtheria, uremia, severe liver disease and excessive vagal stimulation This type of auriculoventricular blocking is called first degree block and results from a simple retardation of the impulse in its transmission to the ventricles This sluggishness is manifested by a prolongation of the P-R interval beyond the usual upper limit of the normal average

time of two-tenths of a second. One of the most frequent signs of digitalis activity is first seen in this prolongation of the P-R conduction time (Fig. 4)

#### Diagnostic Importance of Prolongation of P-R Interval in Rheumatic Fever

The P-R interval prolongation measured in the electrocardiogram acquires particular significance in its relation to rheumatic fever (Fig. 5). It is commonly present in rheumatic carditis, whether the major effects are valvular, myocardial, or pericardial. While in the younger child the valvulitis (in the absence of pericarditis) presents the focalizing signs, the electrocardiogram through the P-R interval prolongation shows the acute rheumatic myocarditis. The evidence of myocarditis, of course, is usually found in all of the symptoms and signs and associated laboratory evidence. However, in the young adult in his first attack of rheumatic polyarthritis, the evidence of valvulitis frequently never develops and the importance of the P-R interval prolongation is particularly significant of acute rheumatic myocarditis. The child develops valvulitis because of the vascularity



Fig. 5—P-R interval prolongation noted in rheumatic myocarditis

of his valves. Aschoff nodules develop close to small blood vessels. Adults possess avascular valves, hence the absence of rheumatic valvulitis during the initial rheumatic attack in adulthood. In both child and adult, however, the widespread signs of rheumatic fever are found in the rheumatic myocarditis presented clinically, but often graphically, and occasionally graphically alone, in the prolongation of the P-R interval. This evidence clears eventually and in practically all patients it disappears entirely as one would naturally expect from the development of the microscopic scar of a healed Aschoff nodule in the myocardium.

The diagnostic importance of the prolonged P-R interval is also appreciated in the presence of vague mild muscular pains without pronounced signs of the systemic evidence of rheumatic fever such as elevated temperature and pulse rate, anemia, in-

creased sedimentation rate and raised white blood count. Again, rheumatic fever without pronounced focal cardiac signs and symptoms flares up during or shortly after acute infectious diseases, such as scarlet fever, measles, upper respiratory disease with acute otitis media, and pneumonia, and the P-R lengthening aids in the diagnosis of rheumatic myocarditis. An occasional case of mono-articular arthritis of acute variety can be diagnosed as of rheumatic fever origin by the recognition of P-R interval prolongation beyond the normal two-tenths of a second.

Thus Mrs M M, a colored woman aged twenty-six, was admitted April 23, 1943, with a history of fever, pain, throbbing and swelling with tenderness of the left knee of two weeks' duration. She had a similar episode with the left elbow, one month prior to entrance to the hospital. She was a known diabetic for five years, the disease being controlled by 40 units daily of protamine zinc insulin. She was in the fourth month of her fourth pregnancy. Moderately severe secondary anemia existed. While she was under observation during the first few days a systolic murmur appeared at the apex. All serologic data including complement fixation for Neisserian infection as well as smears and aspiration of the knee joint were negative. While infectious arthritis appeared as the most probable conclusion, a bifid or mitral P wave was noted as well as a P-R interval of 0.28 of a second. This on subsequent electrocardiograms reached 0.34 of a second. Salicylates and bed rest with local heat to the knee produced gradual improvement, although the patient was in bed for three months. Complete restoration of the knee joint occurred with complete disappearance of all evidence of cardiac involvement, including the electrocardiographic signs. The patient was discharged to the prenatal and diabetic clinics for further care.

#### SECOND DEGREE HEART BLOCK (PARTIAL HEART BLOCK)

In second degree heart block the defect in conduction is manifested by an occasional failure of the ventricle to contract due to lack of the impulse to get through from the auricle to the ventricle. This may occur as a progressive prolongation of the P-R interval until it is so lengthened that a dropped ventricular beat occurs. This is known as a *Wenckebach periodic beat* (Fig 6) and is most commonly encountered in rheumatic myocarditis.

In partial heart block, as second degree heart block is known,

## HEART BLOCK

increasing difficulty is noted in the ability of impulses to get through the conducting system. While ready recognition is easily attained by graphic means, clinical diagnosis can be ascertained without undue difficulty by combining auscultation with palpation of the pulse. In the higher grades of partial heart block the dropped beat may occur regularly, appearing at every eighth, seventh, sixth (and so on) interval of ventricular activity. It is then known as a 9:8 block, or 8:7 block, and so

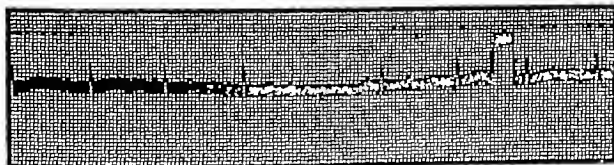


Fig. 6—Progressive prolongation of the P-R interval until a ventricular contraction does not occur. Produced by rheumatic fever and known as the Wenckebach phenomenon.

forth. However, in rheumatic fever, in digitalis overaction and in coronary disease, dropped beats may recur at very irregular and unpredictable intervals. Then graphic registration may often be necessary.

### BUNDLE BRANCH BLOCK

In the early experimental work on animals, right and left bundle branch block was described in the resulting electrocardiograms obtained upon the section of the respective branches of the auriculoventricular bundle. Complete reversal of interpretation has, however, resulted from experimental and clinical evidence within the last decade. Bundle branch block is an electrocardiographic diagnosis. While suggested by split or slurred first or second sound with or without gallop rhythm, graphic registration is necessary. Often, no clinical evidence whatever is presented and it becomes an accidental diagnosis because the electrocardiograph was employed. It is a symptom and not a disease. While most often encountered in the arteriosclerotic processes in the coronary artery system, rheumatic fever and rarely syphilis and congenital heart lesions are the most common known agents producing this type of block. Hypertension with left ventricular strain often accompany or precede the development of the arteriosclerosis of the coronary arteries, particu-

larly where left bundle branch block is found. Acute coronary occlusion is a frequent cause of this type of conduction disturbance.

Histologic studies indicate extensive fibrotic lesions invariably present in both branches of the auriculoventricular bundle in either right or left bundle branch block. Considerable dam-

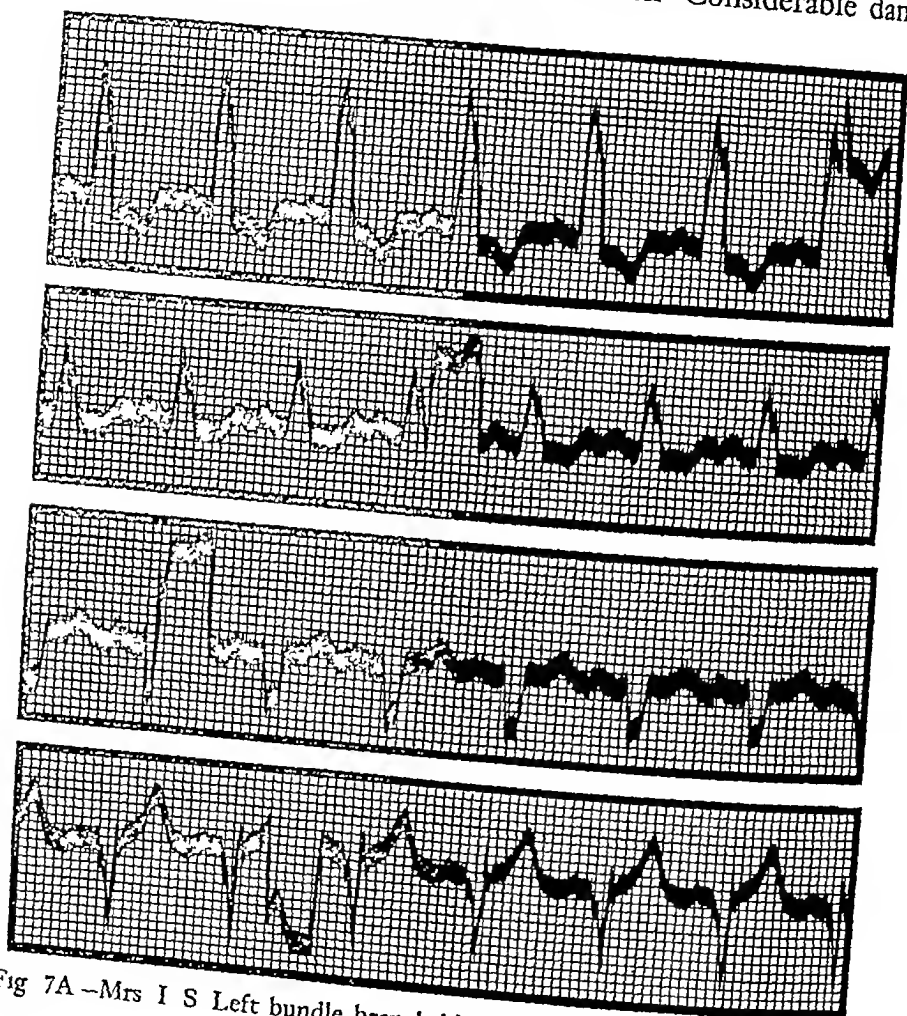


Fig 7A—Mrs I S Left bundle branch block concordant seen in June, 1937

age, however, may be present without pronounced changes or only minor evidence in the electrocardiogram being apparent. Conversely, considerable distortion may be present such as classical bundle branch block in which only a small artery is involved or a small focal lesion exists in the appropriate bundle. Classical bundle branch block, often referred to as *concor-*

*damt* type, characteristically shows the main QRS deflection opposite to each other in Leads I and III with a duration greater than 0.1 second and their respective T waves opposite to the main QRS deflection. Atypical or incomplete types recognized as *discordant* graphs do not possess the characteristic T wave conformity. Wilson has directed attention to the intraventric-

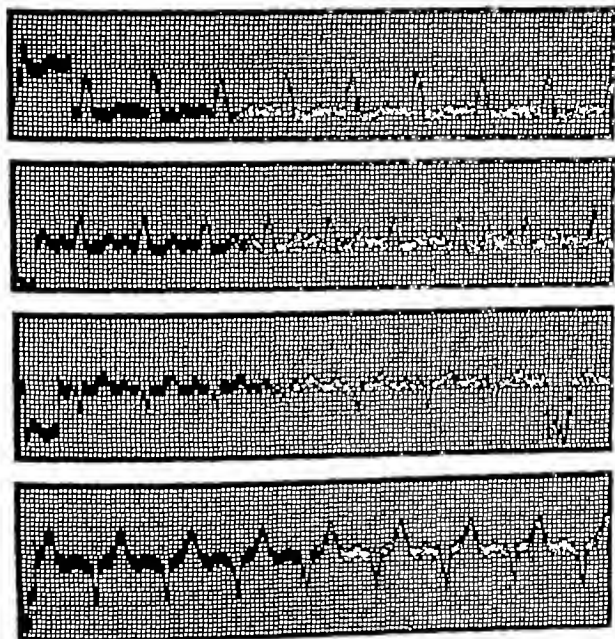


Fig. 7B—Mrs. I. S. Electrocardiogram in February 1943

ular block with the sharp high R wave in Lead I followed by the wide slurred S wave. Wolf, Parkinson and White describe the clinical syndrome of attacks of paroxysmal tachycardia with normal ventricular complexes occurring in classical bundle branch block showing short P-R intervals.

Serious generalized cardiac disease is usually indicated in the presence of the various types of bundle branch block, espe-

cially in the classical variety Nevertheless, reasonably good health can be expected in many patients for many years The outlook is less favorable in those developing the evidence during an acute coronary artery occlusion producing the symptomatology and evidence of acute myocardial infarction Many exceptions are encountered to this general rule, however

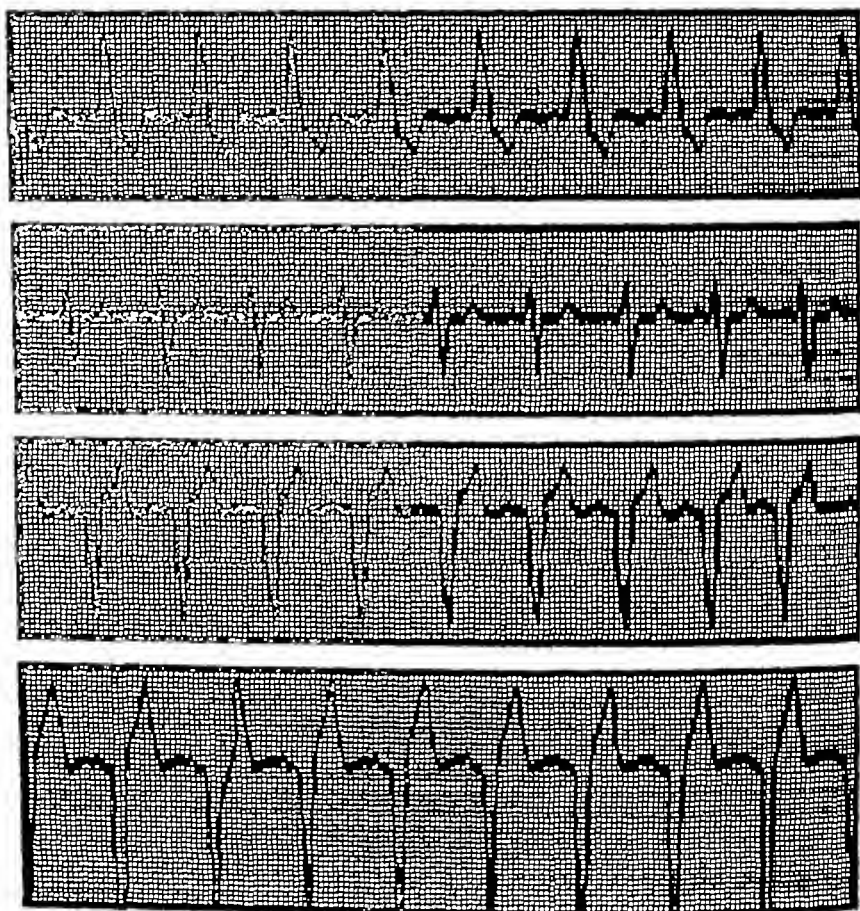


Fig 8—Mrs J P Left bundle branch block concordant, April 29, 1938  
Patient active and continuing household duties, September 6, 1943

Figure 7 shows the left bundle branch block found in Mrs I S at the age of forty-seven years in 1937, and again her graph six years later with reasonably good health and almost no restriction of her physical activity in ordinary household activities and duties

Figure 8 shows the graph of Mrs. J P, aged fifty-one years,

taken on April 29, 1938 Classical left bundle branch block with concordant graph is seen She today cares for her household, but is restricted somewhat in her more strenuous activities

Figures 9, 10 and 11 show right bundle branch block with concordant graph, bundle branch block with wide S pattern



Fig 9—Mr L. S., aged forty-one years Right bundle branch block concordant

in Lead I and intraventricular conduction deformity with wide S pattern respectively

The observation must be made that complete consideration of symptomatology and all collateral evidence is frequently necessary to determine both the etiologic as well as the prognostic



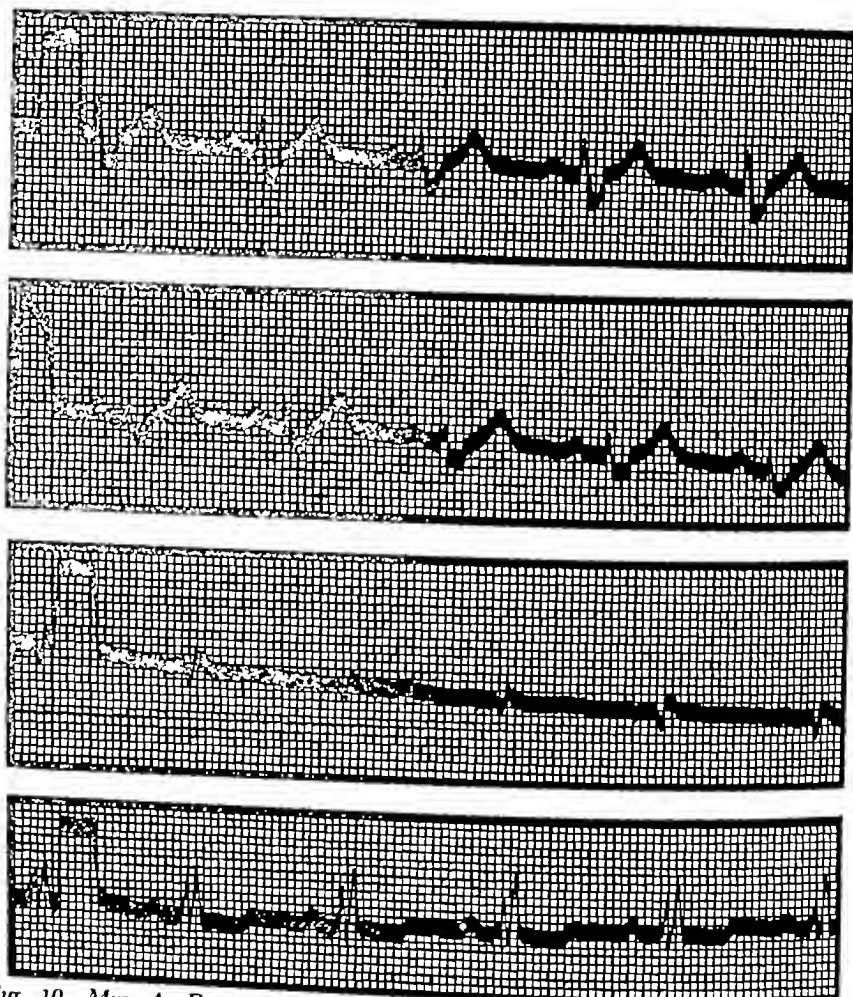


Fig 10—Mrs A F, aged fifty-three years Bundle branch block with wide S pattern in Lead I

and therapeutic implications. Etiologic diagnosis, subjective and objective symptoms together with the electrocardiogram will frequently determine prognosis and therapy in the many and various types of auriculoventricular block.

Occasionally, the evidence presented of the heart's ability to withstand function strain and of good cardiac muscle reserve

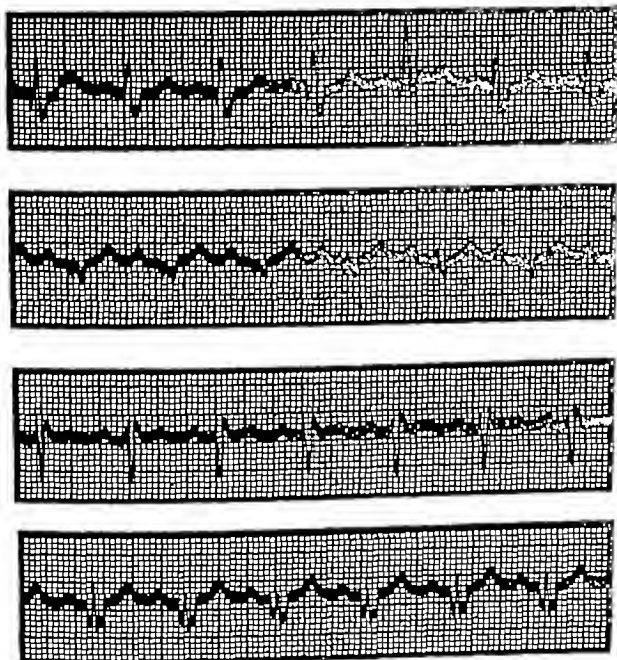


Fig 11-J H., aged sixty-three years. Wide S pattern with intraventricular conduction deformity

far outweighs the seriousness of electrocardiographic signs of auriculoventricular blocking. Nevertheless, sudden death occurring in a patient with minimal electrocardiographic variation, the importance of which has been minimized, is, to say the least, very disturbing to the conscientious clinician.

# SYPHILITIC AORTITIS AND ANEURYSM\*

AARON ARKIN, Ph D, M D, F A C P †

## CARDIOVASCULAR SYPHILIS IS PREVENTABLE

SYPHILITIC heart disease is today the only form of heart disease which is preventable. A more general recognition of this fact will lead to a careful search of all patients infected with syphilis for the early manifestations of this most fatal form of the disease. A diagnosis in the primary seronegative stage by darkfield examination, followed by two years of proper treatment, would prevent at least 90 per cent of cases of cardiovascular syphilis.

I wish in this clinic to discuss the pathology and diagnosis of syphilitic aortitis. Syphilis is responsible for about 20 per cent of cases of chronic cardiac disease found in adults. About one-fifth of all persons who acquire syphilis develop cardiovascular disease. The average length of time from infection to the onset of symptoms is about fifteen years. In luetic aortic regurgitation the average latent period is twenty years, in aneurysm twenty-two years. At necropsy we find that 75 per cent of persons with visceral lues have an aortitis. It is therefore obvious that many of these individuals do not develop clinical evidence of heart disease, and are not diagnosed during life. We shall emphasize the methods at our disposal for the early diagnosis of uncomplicated syphilitic aortitis.

## SEX AND RACE INCIDENCE

There is a marked preponderance of the male sex in the entire picture of syphilis of the heart and aorta. About 80 per cent of the patients are males, yet there is no marked difference in the frequency of luetic aortitis in the two sexes. In females the disease takes a more benign course. The severe supravalvular forms

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\* From the Department of Medicine, Cook County Hospital

† Professor of Medicine and Chairman of Department of Medicine, Cook County Graduate School, Associate Professor of Medicine (Rush), University of Illinois College of Medicine, Attending Physician, Cook County and Mt Sinai Hospitals, Staff, Wesley Memorial Hospital

with aortic regurgitation, stenosis of the coronary ostia, and aneurysm are much more common in men

Syphilitic heart disease is about four times as frequent in the Negro as in the white. Aneurysms are twice as common as in the white race. The greater number of hard laborers, high incidence of hypertension, and more frequent neglect of proper therapy may explain this difference. I believe that there is a more marked involvement of the media with more extensive necrosis in the colored race. While aneurysm is rare in white women we find it not infrequently in Negro women.

#### PATHOLOGY OF SYPHILITIC AORTITIS

Syphilitic aortitis is the basic lesion from which the manifestations of cardiovascular syphilis develop. It leads to aneurysm formation, widening of the aortic ring with separation of the cusps at the commissures and aortic regurgitation, and stenosis of one or both coronary ostia.

Luetic infection usually occurs in the twenties, yet the highest incidence of symptoms due to aortitis is near the forty-fifth year. The reason for this long latent period of twenty years is the very slow progress of the chronic inflammatory process which begins in the vasa vasorum of the adventitia and media. These small vessels undergo obliterative changes which furnish partial anaerobic conditions for the growth of the spirochetes in the media. There is an infiltration by round and plasma cells. The elastic fibers are destroyed by the development of miliary gummas. The destructive and inflammatory changes in the media lead to intimal wrinkling and puckering. The inner surface of the aorta becomes wrinkled and depressed by small and large fibrous scars of pinkish or white color. Atheromatous changes are often combined with the luetic aortitis in an amount increasing with age. The mouths of the large branches of the aorta, such as the innominate, carotid, and subclavian, are often fibrosed and greatly constricted or almost occluded. Thus stenosis of the ostia of the large arteries is of great value in diagnosis, leading to pulse differences, thrills and murmurs along the course of the vessels. Sometimes there is a complete absence of the pulse in one or more large arteries.

#### ANEURYSM FORMATION

As the aortic wall (in some cases also the innominate, carotid, subclavian or other large artery) loses its elastic layer the wall

becomes weakened. It stretches under the influence of the blood pressure. If the mesaortitis is widespread there may be a diffuse dilatation of the ascending, arch, descending or entire thoracic aorta. When the destruction is limited to a small area a saccular aneurysm may develop. Such aneurysms of the thoracic aorta are practically all luetic, whether atheromatosis be present or absent. Multiple aneurysms of the thoracic aorta are quite common.

Aneurysms occur in about 20 per cent of cases of syphilitic aortitis. They are most common in the ascending aorta and arch, and decrease in frequency toward the bifurcation. They tend to occur along the path which receives the impact of the blood column. This pathway runs in the middle of the anterior wall of the supra-avalvular portion, then to the right in the ascending, horizontally in the arch, and along the posterior left aspect of the descending arch, and in the middle of the posterior wall of the descending aorta. They may erode the spine, ribs or sternum.

We shall see that the demonstration of a widening of any part of the thoracic aorta is the earliest diagnostic sign of syphilitic aortitis. Such a widening can often be found before the development of aortic regurgitation, aneurysm, or angina pectoris. Syphilitic aortitis without dilatation of the aorta, regurgitation, or coronary stenosis cannot be diagnosed clinically.

When the orthodiagraphic measurement of the aorta exceeds the normal values, syphilitic aortitis must be suspected. This is especially so when the patient has a positive serologic test, Argyll-Robertson pupils, absent patellar reflexes, or any other evidence of lues.

Hypertension, rheumatic aortic regurgitation, isthmus stenosis, or thyrotoxicosis may lead to increased cardiac force or output with moderate widening of the aorta. With old age the aorta elongates, the arch rises and the vessel becomes more tortuous. There is evidence of atheromatosis, and the process is quite uniform. These conditions can usually be distinguished from luetic aortitis.

Aneurysm may be caused by bacterial emboli in bacterial endocarditis. It is very rare in rheumatic fever. Periarteritis nodosa, suppuration, tuberculosis and trauma are rare causes. Aortic rupture or dissecting aneurysm is usually the result of cystic media necrosis, first described by Erdheim. Abdominal aneurysm may be due to arteriosclerosis.

## AORTIC REGURGITATION

Perhaps the most important pathologic change is aortic regurgitation. This is found in about 75 per cent of the cases diagnosed clinically, and in about 30 per cent of cases of luetic aortitis at autopsy. Syphilis has a special affinity for the sinuses of Valsalva and the aortic ring. The increased strain upon this region caused by the closure of the aortic cusps in diastole is a factor in producing the stretching of the ring. The cusps become thickened at the commissures and are separated from each other. No vegetations are produced, hence there is never a stenosis of the aortic ostium. The ring is stretched, the cusps are too small to close the lumen in diastole and regurgitation results. There is later a regurgitation at each of the commissures, and in the center of the lumen.

*Syphilitic aortitis, therefore, causes only one valvular lesion, aortic regurgitation, never a stenosis.* Rarely, syphilitic pulmonary arteritis causes a pulmonary regurgitation. The mitral and tricuspid valves are not affected. With regurgitation there is a progressive dilatation and hypertrophy of the left ventricle, often leading to great cardiac enlargement. The average length of life is about three years.

## STENOSIS OF THE CORONARY OSTIA

*Another important change is stenosis of the ostia of the coronary arteries.* This is a very frequent finding, a part of the aortitis in the sinuses of Valsalva. It leads to anoxemia of the heart muscle with angina pectoris. The anginal attacks are usually of long duration. The T wave is often negative in Leads I and II of the electrocardiogram. Myocardial failure which reacts poorly to all medication is the end result. The stenosis is so gradual that one ostium may be totally occluded without producing clinical symptoms or any gross myocardial changes. During the years that elapse there is plenty of time for the collaterals to enlarge so that the heart muscle gets its nourishment from the other coronary. When both coronaries are affected the heart may be unable to undergo much hypertrophy. The heart muscle may still receive some blood supply from the thebesian channels, or from anastomoses between the coronaries and vasa vasorum or bronchial arteries.

Sometimes the coronary ostium is covered by a small flaplike thickening of the intima. The presence of an aortic regurgita-

tion reduces the blood flow in the coronaries still further by lowering the diastolic blood pressure. Sudden death is not uncommon in such cases of aortic regurgitation with stenosis of the coronary ostia. In very rare cases a supernumerary vessel may furnish blood to the myocardium.

It often appears as if the stenosis of the coronary ostia protects them against atheromatosis by reducing the blood flow and pressure in these vessels. The arteries themselves are not affected in syphilis, hence coronary thrombosis with infarction

CHILDEN.

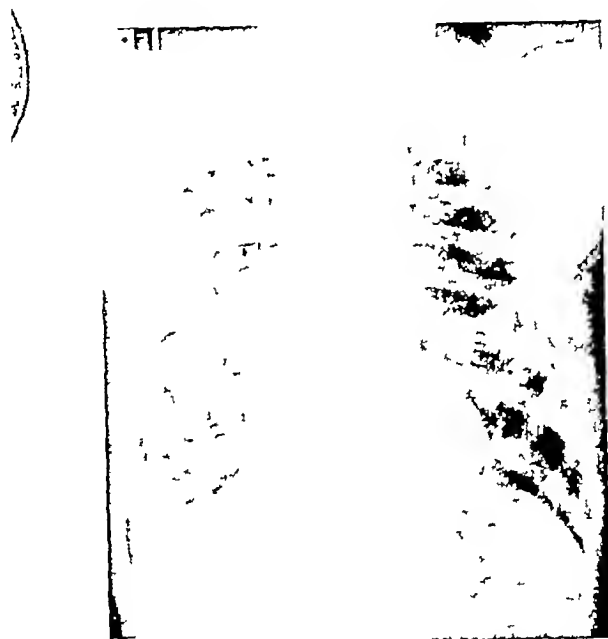


Fig 12—Early syphilitic aortitis, with characteristic convex prominence of the ascending aorta. There was a typical tambour aortic second sound, heard best in the second right interspace. There was no regurgitation, hence the heart is normal in size. The Kahn test was positive.

is uncommon. When it does occur it is usually the result of sclerosis or subintimal hemorrhage.

The heart muscle is only rarely affected by syphilis. Seldom is a gumma or diffuse syphilitic myocarditis found. In the bundle of His it may lead to heart block. In a papillary muscle rupture may occur. The fibrous changes found in older luetic individuals are more readily explained as a result of arteriosclerotic nonluetic coronary disease, or ischemia of the muscle from the stenosis of the ostia.

It must be emphasized here that aneurysm alone does not cause cardiac enlargement, regardless of its size. In the absence of aortic regurgitation, coronary disease, hypertension or other cause, the heart remains normal (Figs 13, 15, 20) Aneurysms of the supra-avalvular portion of the aorta may rupture into the pericardial sac, causing death from heart tamponade Syphilitic aneurysm is not likely to lead to a dissecting aneurysm because of the inflammatory changes in the media and adventitia It often compresses the trachea, left bronchus, esophagus, pleura, or lung It may rupture into any adjacent structures

#### DYSPHAGIA AND LEFT HEMOTHORAX

I have in the past few months seen three cases of aneurysm of the arch with compression of the esophagus and marked dys-



Fig 13

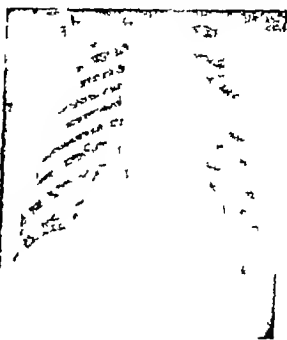


Fig 14

Fig 13—Aneurysm of the arch of the aorta with marked compression and displacement of the trachea and esophagus. The patient had marked dyspnea, an asthmatic wheeze cyanosis and dysphagia. He could not even swallow liquids. There was no aortic regurgitation, hence heart is normal in size. The diagnosis was made clinically from the history and physical examination

Fig 14—Same patient as Figure 13 with barium in esophagus. Note the marked displacement of the esophagus to the right with a complete occlusion. The patient died three weeks later of a perforation of the aneurysm into the esophagus (autopsy)

phagia (Figs 13, 14, 15, 20) In two of the cases swallowing became impossible One patient died of perforation into the esophagus, another of tracheal compression (Figs 14, 15)



We have had five cases of aneurysm of the descending aorta with dysphagia. In three there was also erosion of the spine. Four years ago I had under observation a patient with a syphilitic aneurysm of the right subclavian artery with marked erosion of the right clavicle, and clubbed fingers of the right hand (Fig 25)

We have had five cases of aneurysm of the arch and descending aorta with left hemothorax. In one there was an accompany-



Fig 15—Aneurysm of the arch of the aorta with marked dysphagia. Note the marked dilatation of the aortic arch, with an aneurysm of the descending portion pointing to the right and occluding the esophagus. There was no aortic regurgitation. The diagnosis was made clinically from the history of dysphagia, a tracheal tug, and visible pulsation in the left sternoclavicular region. The case is quite similar to that in Figures 13 and 14. Both were in my ward at the same time.

ing atelectasis of the left lung from occlusion of the left bronchus (Figs 22, 26, 27). I have for several years recognized this as a definite clinical entity.

One interesting case of aneurysm involved the left sinus of Valsalva. There was an aortic regurgitation. The film revealed a prominent pulmonic knob due to displacement of the pulmonary artery by the aneurysm (Fig 24). The diagnosis was confirmed at autopsy. In such cases there is usually an aortic



Fig 16.



Fig 17

Figs. 16 and 17—Syphilitic aortitis with aortic regurgitation and huge aneurysm of the lower thoracic aorta. The aneurysm eroded the ribs posteriorly on the left side producing a large pulsating mass. It dissected the diaphragm. Note the erosion and sclerosis of the tenth, eleventh and twelfth dorsal vertebrae with destruction of the attachment of the eleventh and twelfth ribs. The twelfth rib is displaced downward.



Fig 18



Fig 19

Fig 18—Large calcified aneurysm of the descending arch of the aorta. Note the widened and calcified descending thoracic aorta just below the large sac.

Fig 19—Aneurysm of the innominate artery, associated with early luetic aortic regurgitation and slight cardiac enlargement. The diagnosis was made from the physical findings. There was a pulsating mass in the right supra clavicular fossa, a tracheal tug and marked dyspnea.

regurgitation The pulmonary artery, interventricular septum, right or left atrium may be displaced or compressed

Another case of aneurysm of the abdominal aorta led to a very marked hypertension The aneurysm, in a colored man aged twenty-one, was produced by a gumma of the media The hypertension was most likely due to partial occlusion of one renal artery by the aneurysm

### SYMPTOMS OF ANEURYSM

The most common symptom of aneurysm is *pain* This is usually due to erosion of bony structures, or pressure on nerve trunks (Figs 17, 21, 25) When a stenosis of the coronary ostia develops, angina pectoris also occurs I have often emphasized in clinics that there are two important causes of persistent thoracic



Fig 20



Fig 21

Fig 20—Large saccular aneurysm of the descending thoracic aorta with backache and dysphagia Note the dilated aorta below the sac, visible through the heart shadow There was no aortic regurgitation, hence no cardiac enlargement

Fig 21—Same patient as Figure 20, lateral view Note the large aneurysmal sac, and the definite erosion of the seventh and eighth thoracic vertebrae.

pain in adults, namely pulmonary neoplasm and aneurysm In many cases the diagnosis of aneurysm is made by mere inspection of the anterior and posterior chest wall There may be a visible pulsation in the painful area in the sternal, parasternal, or left paravertebral regions This plus a tracheal tug or difference

in the radial pulses, or an aortic regurgitation, makes the diagnosis very easy. Yet the roentgenographic findings based only on a film may be very confusing, especially with atelectasis of an entire lung or a hemorrhagic pleuritis, or unsharp outline of the aneurysm due to infiltration of adjacent structures with blood (Figs 22, 26)

*Dyspnea* due to tracheal or bronchial compression is the next most common symptom. Not only is the trachea or bronchus displaced or compressed, but the cartilages may be destroyed with collapse and death from asphyxia. Often the patient assumes



Fig 22

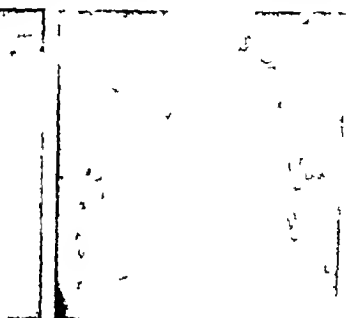


Fig 23

Fig 22—Large aneurysm of the entire arch of the aorta with left hemothorax. Aspiration yielded bloody fluid. A diagnosis of slow bleeding into the pleura was made clinically and confirmed (autopsy)

Fig 23—Large saccular aneurysm of the ascending aorta, with diffuse dilatation and some atheromatosis of the arch and descending thoracic aorta. There was no aortic regurgitation, hence the heart was not enlarged

an odd position in which he gets some relief. Recently I had a patient with an aneurysm of the arch who was more comfortable on his stomach in an opisthotonos position, which he occupied most of the time. Others lie on the left side, or assume a knee-chest position.

*Cough* is the third most frequent symptom, often accompanied by hoarseness. The cough is persistent, leading to marked cyanosis. I have found *dysphagia* much more common than textbooks and articles on aortitis indicate. *Hoarseness* due to involvement of the left recurrent laryngeal nerve often occurs with large aneurysms of the aortic arch.



Fig 24

Fig 24—Syphilitic aortitis with aortic regurgitation and aneurysm of the left sinus of Valsalva. Note the prominent pulmonary artery, displaced by the aneurysm (autopsy)



Fig 25.

Fig 25—Aneurysm of the right axillary artery due to syphilitic arteritis. Note the circular erosion of the clavicle. There was marked clubbing of the fingers of the right hand. Operation was performed with ligation of the artery



Fig 26

Fig 26—Large aneurysm of the aortic arch with compression of the left bronchus, atelectasis of the left lung, and left hemothorax.



Fig 27

Fig 27—Findings after aspiration of the left chest. Note the large aneurysm of the arch and the atelectatic left lung

A roentgenographic study consisting of careful fluoroscopy and films in various positions is of the greatest value. The pres-

ence of dilatation of other parts of the aorta may be decisive in a differential diagnosis (Fig 20)

*Aneurysm of the innominate artery* may be diagnosed by finding the throbbing in the right supraclavicular fossa, a palpable pulsating mass, a thrill, often a diminished right radial pulse, pressure upon the trachea, and a tracheal tug (Fig 19)

*Aneurysm of the abdominal aorta* will be diagnosed more frequently if the abdomen is carefully palpated in all luetics, especially those with thoracic aneurysm. Although some may be arteriosclerotic, the majority of abdominal aneurysms are due to syphilis. Abdominal pain, a pulsating expansile mass, and roentgenographic evidence when accompanied by atheromatosis make the diagnosis easy in most cases. The aneurysm may lead to hypertension by causing renal ischemia, may erode the spine, compress or split the diaphragm, lead to embolism of the mesenteric artery, or may rupture.

#### DIAGNOSIS OF SYPHILITIC AORTITIS

In luetic aortitis the diagnosis is of greatest value to the patient in the early uncomplicated stage, before aortic regurgitation, aneurysm, or angina pectoris has developed. I shall, therefore, stress the signs which I have found most useful in the diagnosis of uncomplicated aortitis.

In the first few years after the primary infection a clinical diagnosis of syphilitic aortitis is usually not possible, although histologic changes may already be present.

The earliest and most important diagnostic sign is a *widening of the ascending aorta, or any other part of the aorta, on fluoroscopic examination*. An examination of hundreds of normal as well as syphilitic aortas will give the observer a good idea of the normal size of the aorta in persons of various size and weight.

The entire contour of the ascending, arch, and part of the descending aorta can be very quickly observed by the trained examiner. Unfortunately we are unable to visualize the first inch or more of the aorta, including the aortic ring, where syphilis does its greatest harm.

A convex prominence of the ascending aorta, often with increased pulsation in this area, is quite characteristic (Fig 12). An ascending aorta more than 3 to 4 cm in diameter in an adult should be suspected of being luetic. This is especially true when the patient has a positive serologic test, Argyll-Robertson pupils

absent patellar reflexes, tabes or paresis Unfortunately, only about 75 per cent of patients with cardiovascular syphilis have a positive Wassermann or Kahn test, a negative test thus occurring in about one fourth of the cases.

In the right oblique position the ascending aorta can be measured quite accurately Its increased diameter, convex prominence to the right, and increased density proportional to its dilatation make the diagnosis The aortic knob on the left is often enlarged and extends farther upward and to the left Giving barium paste enables one to measure the descending portion of the arch, from the concavity in the esophagus wall to the left border (Kreuzfuch's method) The normal symmetry is often disturbed, and the arch becomes asymmetrical It must be remembered that aortitis and atherosclerosis are frequently combined It is never safe to assume a marked dilatation as due to atheromatosis or hypertension A definite aneurysm of the ascending aorta or arch is practically always luetic

The patient should be rotated in the left as well as right oblique position Any departure from the cylindrical form is significant

The second most important sign in aortitis without regurgitation is *the increased and widened manubrial dulness on percussion, especially to the right* There may be a slight pulsation in the second or third right interspace on deep exhalation, or the second or third left interspace

The third most frequent finding is the *tambour or bell-like, ringing, aortic second sound* first described by Potain This peculiar musical quality may be due to the increased tension on the aortic cusps produced by stretching of the ring The heart sounds are often unusually well transmitted because of the thinning of the lung by the expanding aorta. The aorta lies in contact with the chest wall The tambour second sound is heard in a small area, usually to the right of the sternum To the trained ear the tambour second sound is diagnostic of uncomplicated syphilitic aortitis It may be present before there is any demonstrable widening of the aorta, thus being the earliest sign of aortitis

A fourth frequent finding is *a 'systolic murmur at the base*, found in about two thirds of the cases of uncomplicated aortitis, and in practically all the cases of aortic regurgitation accompanying the diastolic murmur. The murmur is often harsh and

heard best in the second right or left intercostal space near the sternum. It must be remembered that a systolic murmur at the base is a frequent finding in patients past middle life, due to atheromatosis or sclerosis of the cusps in the absence of aortic syphilis. Therefore, a systolic murmur alone is not diagnostic of aortitis. I believe that the systolic murmur in syphilitic aortitis is more likely due to the stretching of the aortic ring with increased tension upon the cusps in systole. This prevents them from approximating the wall of the aorta. The projection of the cusps under tension produces the systolic murmur. It persists after separation of the cusps, hence the double murmur of aortic regurgitation.

A fifth sign in the diagnosis of syphilitic aortitis is the *pulsus differens*, or even total absence of pulsation in one or more of the main branches of the aorta (innominate, left carotid, left subclavian). When the left carotid and subclavian pulse, or only the subclavian, is weaker than the right an isthmus stenosis must be considered. This is usually not difficult to diagnose, especially when the blood pressure in the lower extremity is low and the ribs reveal the characteristic erosions.

Inequality of the radial pulses is common in aortitis. All three ostia of the main arteries may be involved, as in one of my cases. There was no pulsation in either arm or the right carotid. There was a systolic murmur and thrill over the left carotid. Our diagnosis was a luetic aortitis with occlusion of the ostium of the innominate and left subclavian arteries, and stenosis of the ostium of the left carotid. This was confirmed at autopsy. There was also an anomalous vertebral artery coming from the aortic arch.

A sixth sign of syphilitic aortitis is the *presence of an aneurysm of any part of the thoracic aorta*. We have seen a number of aneurysms of the innominate artery.

*Angina pectoris* is quite frequent in luetic aortitis. It is usually of a severe type and progressive. The pain is due to the stenosis or occlusion of the coronary ostia. Another factor is the lowering of the diastolic blood pressure when aortic regurgitation develops. A certain number of the patients have hypertension with cardiac hypertrophy. The increase in the volume of the heart muscle causes a still greater demand for oxygen at the same time that the blood supply is being slowly reduced.

Another sign of value is the presence of a *suprasternal pulsa-*



tion, due to dilatation and elongation of the aortic arch. At times the dilated aortic arch may be palpable in the episternal region.

### DIAGNOSIS OF AORTIC REGURGITATION

Aortic regurgitation, the only valvular disease caused by syphilis, except for the rare pulmonary regurgitation, is seen most often in the fifth and sixth decades. Occasionally we find it before the age of thirty-five years. The diagnosis of aortic insufficiency is usually an easy matter.

First and most characteristic is *the diastolic murmur at the base*. In the early stage it may be missed unless one listens carefully during forced exhalation with the patient leaning forward. It may be heard in the aortic area, in the second or third right or left interspace near the sternum. As the disease progresses and the aorta dilates, the latter lies close to the chest wall to the right of the sternum, hence the murmur in advanced cases is often loudest in the second and third right interspaces. There is usually an accompanying *systolic murmur*, which I believe is best explained as due to tension on the cusps so that they cannot approximate the aortic wall during the systole.

Later there is a disappearance of the aortic second sound and only the two murmurs are heard. The pulse pressure increases, and the heart enlarges especially to the left. In the majority of cases the lesion can be suspected from the *elevated systolic and lowered diastolic pressures*. There are few other causes of increased pulse pressure, namely, thyrotoxicosis, senile arteriosclerosis, and total heart block.

Frequently the diagnosis can be made at a distance by noting the hopping carotid arteries with synchronous vibration of the head. The *Corrigan pulse* and *Duroziez sign* on compression of the femoral or other large artery are quite characteristic. A capillary pulse is often present, but not diagnostic as we see it in other conditions.

In the past twenty years I have seen three cases of luetic aortic regurgitation with an unusually loud musical diastolic murmur associated with a diastolic thrill. The thrill was most marked in the second or third right intercostal space. I have offered as one explanation for this unusual murmur and thrill the presence of a fenestrum of one or more of the aortic cusps.

### Differential Diagnosis between Luetic and Rheumatic Regurgitation

The differential diagnosis between luetic and rheumatic aortic regurgitation may be difficult in exceptional cases. The presence of an associated organic mitral lesion speaks for rheumatic endocarditis. The same is true when an aortic stenosis is present. An aortic regurgitation, therefore, in the absence of any other organic valvular disease in an adult, is most likely luetic. The presence of aortic dilatation or aneurysm makes the diagnosis quite certain, even in the 25 per cent with a negative Wassermann or Kahn test.

I have seen three cases of combined rheumatic and luetic disease in which the diagnosis of both types of lesion was possible. In two there was a definite stenosis of the aortic ostium, which is never luetic, associated with an aortic aneurysm. In one there was an old rheumatic mitral stenosis and regurgitation, a history of chancre twenty-five years ago, and a luetic aortic regurgitation with an aneurysm of the ascending aorta. In rare cases a bacterial endocarditis may be engrafted on a syphilitic aortic valve.

In the absence of a widening of the aorta, of a positive serologic test or other evidence of syphilis, or of other valvular disease, it would be impossible to say whether the lesion is luetic or rheumatic. To state that syphilitic and rheumatic or syphilitic and subacute bacterial disease do not occasionally occur in the same patient is incorrect. I have seen such combinations several times both clinically and at necropsy.

### CONCLUSION

In conclusion, I wish to emphasize the importance of a periodic careful physical examination and roentgenographic study, for the presence of luetic aortitis, of every patient with evidence of syphilis. The diagnosis of uncomplicated aortitis is possible in a considerable percentage of all cases.

The most valuable aids are (1) careful fluoroscopic examination, (2) tambour aortic second sound, (3) increased manubrial dulness especially in the second and third intercostal space, (4) visible pulsation in the second or third intercostal spaces or suprasternal, (5) difference in the radial or carotid pulses, (6) angina pectoris in a young adult in the absence of other cause. An early diagnosis followed by intensive antiluetic therapy will prevent most cases of aortic regurgitation and aneurysm.

# SUBACUTE BACTERIAL ENDOCARDITIS

(Clinic of Dr Robert S. Berghoff\*)

ROBERT S. BERGHOFF, M.D., F.A.C.P.,† ANGELO S. GERACI, M.D.‡  
and

DONALD A. HIRSCH, M.D.§

## PRESENTATION OF A CASE

TODAY, I shall present a patient and discuss in detail a problem of relatively rare occurrence which has assumed considerable importance, however, because of a new approach in the matter of therapy

*The Patient's History*—Our patient, Miss J. T., is twenty-four years old and obviously is acutely ill. Her bedside history reveals the following: At the age of eleven, she had acute inflammatory rheumatism (acute rheumatic fever). The disease ran a typical course—involvement of the larger joints, knees, ankles and elbows, with pyrexia and an early invasion of the heart. Five years later, when she was sixteen years of age, she developed chorea with an acute exacerbation of the heart symptoms and was kept at bed rest for four months. She made a temporary and relative recovery and was able to be up and around and go to school.

She was restricted in her activities, however, and was told that she had "a leaky mitral valve." This was both an interesting and fairly accurate diagnosis, because while acute rheumatic fever, as we all know, is responsible for the vast bulk of acute cardiac valvular disease in youth, it may and does affect both the mitral and the aortic valves. Chorea, on the other hand, has a more specific and selective action and with few exceptions involves the mitral cusps exclusively. Accordingly, the diagnosis of "mitral heart dis-

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\* From the Mercy Hospital—Loyola University Clinics

† Clinical Professor of Medicine, Loyola University School of Medicine, Director of Heart Station, Mercy Hospital—Loyola University Clinics

‡ Clinical Associate in Medicine, Loyola University School of Medicine, Associate Director of Heart Station, Mercy Hospital—Loyola University Clinics (Now Major, Medical Corps, Army of the United States)

§ Clinical Instructor in Medicine, Loyola University School of Medicine, Assistant Director of Heart Station, Mercy Hospital—Loyola University Clinics (Now Captain, Medical Corps, Army of the United States)

case" following both an acute rheumatic infection and five years later a typical chorea, renders the diagnosis of mitral heart disease from the history alone both interesting and logical

For the next seven years, from the age of sixteen to twenty-three, this young lady was relatively free from heart symptoms and was able to carry on a gainful occupation (clerk in a law office) Two months ago she developed a mild sore throat followed by a severe chill and elevated temperature, heart consciousness and dyspnea While her symptoms have subsided, she has been confined to bed An important negative point in her recent history, which I wish to emphasize before passing on to the physical examination, is that she has had no recurrence of her rheumatism or of her chorea—and that in spite of marked exacerbation of the heart symptoms

*Physical Findings*—We are dealing with a young woman who is acutely ill Her color is pallid (a secondary anemia), the lips are cyanosed, and she is dyspneic The temperature is 102° F, the pulse rate is 130, and the respiratory rate while the patient is lying in bed is 30

The heart reveals the following Percussion measurements certified by telefluoroscopy, are right ventricle 6 cm transverse 14 cm. The left auriculoventricular sulcus is "convex" A murmur, pre-systolic in time, is easily audible over the apex and is confined to the fifth and sixth left interspaces In a word, the patient has a well developed and, from extracardiac signs, a decompensated mitral stenosis due to rheumatism and chorea

The lungs and pleura are normal but the liver is definitely enlarged and pulsating More interesting, however is the left hypochondrium where a mass is easily palpable, apparently the spleen The skin over the abdomen reveals a few discrete, pinkish petechiae.

*Laboratory Findings*—Urine shows albumin, pus, casts and red blood cells, blood, a mild secondary anemia with a marked leukocytosis (23,000) Blood culture reveals a nonhemolytic streptococcus with no other organisms

*Diagnosis*—The "actual" diagnosis in this particular instance is simple and certified because of a combination of pre-existing rheumatic and choreic mitral stenosis, a seven-year interval free from cardiac symptoms and from apparent reinfections, and then a sudden acute episode ushered in with sore throat, chill and pyrexia with "entire absence of joint pains or choreic manifestations" Finally, the enlarged spleen, petechiae, and blood culture of non-hemolytic streptococci render the diagnosis of subacute bacterial endocarditis complete

With the diagnosis definitely certified in this particular patient, let us now review (in the absence of the patient) the

general subject of subacute bacterial endocarditis, particularly as regards the prognosis and treatment

### ETIOLOGY

The direct cause of subacute bacterial endocarditis is always the *Streptococcus viridans*. Interestingly, however, this organism never attacks a previously normal heart valve. Subacute bacterial endocarditis is always seen in a valve previously diseased or malformed. Accordingly we encounter the history and physical findings of either a congenital heart lesion or an old quiescent rheumatic heart in all instances. The congenital heart lesions, however, which almost always are found in the right heart as in pulmonary stenosis, patent ductus arteriosus and patency of the interventricular septum, are relatively infrequent as a predisposing factor (less than 5 per cent), the disease usually being implanted on old rheumatic hearts. Here, too, there is some selectivity. The mitral and aortic valves alone or together provide most of the sites for its occurrence. A further interesting point is that a well defined so-called "buttonhole type" of mitral stenosis associated with auricular fibrillation and acute decompensation is rarely complicated by subacute bacterial endocarditis.

In brief, subacute bacterial endocarditis is most frequently encountered in mitral and aortic insufficiencies due to a previous rheumatic endocarditis, and in compensated mitral stenosis with a normal cardiac rhythm. Only infrequently does this disease develop in patients with auricular fibrillation or with symptoms or signs of congestive heart failure.

### PATHOLOGICAL SITE—VALVES INVOLVED

As previously stated, subacute bacterial endocarditis is practically never a primary lesion but one superimposed either on an old congenital valve deformity (which type constitutes possibly 5 per cent or even less of all cases) or upon a previous rheumatic endocarditis. It is interesting to note how percentages of valve involvement differ in the literature. In our experience, mitral lesions predominate over aortic in great preponderance. This seems to us logical, too, for clinical reasons. In the first place, rheumatic endocarditis is more frequently associated with the mitral valve than with the aortic valve. We encounter mitral insufficiency and mitral stenosis, one or the other, or the two

combined, at least three times as frequently as we do an uncomplicated aortic insufficiency, which of itself accounts for the common combination of mitral rheumatic heart disease and subacute bacterial endocarditis.

In the second place, chorea practically limits itself to the mitral valve. We have in our records of more than one hundred cases of endocarditis due to chorea no instance of uncomplicated aortic disease. From our experience, therefore, we feel convinced that in rheumatic and choreic hearts the mitral valve is the valve of choice and frequency in a later subacute bacterial endocardial invasion.

#### DIAGNOSIS

The correct interpretation of disease in an individual who is not only acutely ill but has definite heart symptoms and signs is not so simple as might be anticipated. As a rule, the patient with subacute bacterial endocarditis gives the history of a previous rheumatic endocarditis. After a varying period he has suffered a sore throat or developed a local focus of infection such as an infected tooth, a head cold, or a mild influenza. In a word, an individual, usually youthful, with a history of a previous rheumatic endocarditis, not totally incapacitated, often ambulatory and at work or in school, as a result of a secondary infection suddenly becomes acutely ill with a rapid and progressive exacerbation of cardiac symptoms and signs. Loss of appetite, sweats and alternating mild chills develop and persist in spite of treatment. There is a progressive loss of weight and strength. Elevation of temperature is an early and constant symptom, ranging from a moderate degree of  $100^{\circ}$  to  $101^{\circ}\text{F}$ , to  $103^{\circ}\text{F}$  and even higher as the infection progresses.

As a rule, within two weeks from the advent of a persistent fever, distinguishing *physical signs* appear, which accumulatively have considerable diagnostic significance.

1 *Petechiae*, or hemorrhagic spots, minute, 2 to 3 mm in diameter, appear both on mucous surfaces and on the skin, most commonly on the conjunctivae, the lips, or the skin of the abdomen and chest. They of themselves, if they occur in numbers and persist, speak for a bacterial endocarditis, particularly in the presence of clinical evidence of an endocarditis.

2 An *enlarged palpable spleen* associated with a definite heart murmur in a youthful individual who is obviously acutely and critically ill and who shows no signs of acute cardiac decompensation.

sation such as an enlarged liver or extremity edema, is almost diagnostic

3 *Hematuria*, or more particularly the presence of a very considerable number of red blood cells microscopically in the urine of a youthful cardiopath, in the absence of evidence of a primarily diseased kidney, is very significant

4 My associates and I must take exception to the importance placed in medical literature upon the symptom or sign of *clubbing of the fingers* in subacute bacterial endocarditis. In the first place, in our experience we do not encounter "clubbed fingers" frequently enough in this disease to consider it an important diagnostic sign. Furthermore, we find this "clubbing" and "painful finger tips" in congenital forms of heart disease, in cor pulmonalis, and even in acute bacterial endocarditis, so we have come to consider it a sign of minor diagnostic importance

5 Systemic spread through the agency of *emboli* is of very considerable diagnostic importance. Emboli are very common in the spleen and explain the acute sharp pain complained of in the left hypochondrium and occasionally referred up into the left lower thorax. Less frequently they occur in the kidney and still more seldom in the brain. Occasionally, too, small emboli become dislodged and result in pulmonary infarction. It is important to remember the potential embolic possibilities in subacute bacterial endocarditis

6 *Positive blood culture* of *Streptococcus viridans* (green-producing) is of course diagnostic, because it is rarely isolated in any other form of acute endocarditis. On the other hand, a negative culture is inconclusive, for in an impressive percentage of clinically proven instances of subacute bacterial endocarditis the *Streptococcus viridans* is never isolated

### Differential Diagnosis

The differential diagnosis between subacute bacterial endocarditis and *an acute exacerbation or recurrence of rheumatic endocarditis* can be very confusing for the following reasons: (1) In both conditions a history of a previous rheumatic infection is given. (2) Both show similar physical signs. (3) Both not infrequently run a similar course, with elevation of temperature, acceleration of pulse and exaggeration of heart symptoms and signs.

The following points, however, are helpful in the differential diagnosis

1 A person with subacute bacterial endocarditis is almost always more acutely ill than one with recurrent rheumatic endocarditis, with a higher temperature range, more profuse sweating, and so forth

2 In subacute bacterial endocarditis there is usually no history of recent joint pains or, in the case of a choreic heart, of a return of the choreic symptoms, the heart symptoms and signs alone are in the picture

3 While a leukocytosis is the rule both in subacute bacterial endocarditis and in recurrent rheumatic endocarditis, it is usually decidedly more pronounced in the former

4 Hematuria is the "rule" in subacute bacterial endocarditis and the "exception" in the recurrent rheumatic

5 Finally, petechiae and an enlarged palpable spleen are practically pathognomonic of subacute bacterial endocarditis, and, if obtained, a blood culture of *Streptococcus viridans* certifies the diagnosis.

Occasionally subacute bacterial endocarditis is differentiated with difficulty from *acute bacterial endocarditis* for the following reasons (1) In both conditions the individual is acutely and critically ill, with very definite cardiac symptoms and signs (2) The patient for diverse reasons may be unable to provide the history of a previous rheumatic or choreic infection (3) The disease directly responsible for the acute bacterial endocarditis may be obscure or the organism difficult to isolate

Ordinarily, however, acute bacterial endocarditis can be fairly readily differentiated from the subacute type on the following points

1 The patient with acute bacterial endocarditis not only has heart symptoms and signs but has them as a complication of a severe constitutional disease present at the moment This disease may be a concurrent pneumonia, a tuberculosis, a gonorrheal infection, or any disease due to the pyogenic organisms

2 The patient as a rule is more desperately and acutely ill

3 There is no history and there are no signs of a previous rheumatic heart

4 Petechiae are uncommon

5 The blood culture for *Streptococcus viridans* is negative,



and we may be able to isolate the organism responsible for the acute infection

### PROGNOSIS

I approach this subject with considerable caution and pessimism. It is true that a combination of new therapeutic measures offered within the past few years has, in the medical literature at least, altered the picture so far as the mediate and immediate outlook of these patients is concerned. Possibly the outlook is a bit brighter, particularly as regards the immediate prognosis. Maybe the disease in some of these persons becomes arrested, quiescent, and reinfection is avoided for a considerable time. This is particularly true if, as some writers and clinicians insist, the newer methods of treatment are used not only vigorously but prophylactically as well. However, subacute bacterial endocarditis once fully developed and certified is a fatal disease—not as rapidly fatal as the acute type of bacterial endocarditis, but complete recovery in the experience of my associates and myself is rare indeed.

### TREATMENT

The management of subacute bacterial endocarditis is a controversial subject. As in the case of the prognosis, I feel uncertain and pessimistic regarding the treatment of this type of heart disease. However, in apology I ought to state that in our clinic we encounter subacute bacterial endocarditis not early, not in a preclinical or a prophylactic stage, but, as a rule, only after the disease is well developed. This may in a measure explain why in our own limited experience our results are unsatisfactory.

Our routine treatment of subacute bacterial endocarditis is as follows:

- 1 Absolute bed rest, with no temporizing because of orthopnea, heart consciousness or any other symptom or group of symptoms which might suggest the advisability of semi-invalidism.
- 2 Diet, soft and bland, with fluids to 2000 cc daily, orally preferred, and if not practical, intravenously.
- 3 Fever therapy in the absence of contraindications, but as a rule we prefer radiation heat to the parenteral type (intravenous typhoid, etc.).
- 4 We use the sulfonamides routinely, the types and dosages determined individually.
- 5 A combination of the sulfonamides and heparin frequently has a favorable clinical reaction.

6 General and symptomatic management is important and should include the following (a) Ice bag to the precordium in the presence of a rapid and forceful heart. (b) Sedatives during the day, particularly the barbiturates, and narcotics short of the opium compounds for sleep at night (c) Blood transfusions are helpful and indicated if the total red cell count drops rapidly and progressively under three million In this connection, too, liver therapy orally and intramuscularly has a marked temporary value (d) I have used thiamine chloride intravenously with startling temporary results

### CONCLUSIONS

My associates and I have this morning demonstrated a patient a young woman, with a typical and certified (clinically and by blood culture) subacute bacterial endocarditis We have made the following observations concerning subacute bacterial endocarditis in general

1 It is not a "primary" disease, but both clinically and pathologically it is an implantation upon a heart valve previously malformed (congenital) or diseased (due to rheumatism or chorea)

2 We have reviewed the average clinical course of this disease, both as to symptoms and to signs.

3 We have discussed the diagnosis and differential diagnosis, pointing out the complexities and confusions, particularly between subacute bacterial endocarditis and a recurrent acute rheumatic endocarditis and, less frequently, an atypical acute bacterial endocarditis

4 We stress the fact that, compared with the great number of youthful individuals suffering with acute rheumatic endocarditis, subacute bacterial endocarditis is relatively uncommon, and we do not agree that anywhere near 20 per cent of these patients develop subacute bacterial endocarditis as a terminal complication

5 Finally, I have attempted to give an unbiased opinion concerning both the prognosis and treatment, including the newer methods of chemotherapy and the sulfonamides In our experience, subacute bacterial endocarditis, proved clinically and certified by blood culture (*Streptococcus viridans*), is nearly always a fatal disease We feel that a combination of sulfonamide therapy, thiamine chloride intravenously and blood trans-

fusions definitely improve the clinical picture temporarily, but we are unconvinced that these measures pushed heroically are ever completely effective in curing it.

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## COMMON FORMS OF CONGENITAL HEART DISEASE\*

WRIGHT ADAMS, M D † and DONALD E. CASSELS M D ‡

THE complexity and variety of congenital heart lesions make accurate anatomic diagnosis difficult and in some cases impossible before death. The progress that has been made has come chiefly from the correlation of clinical with autopsy findings. Studies of this kind have been difficult for the clinician primarily because the relative infrequency of the disease and the great variety of the lesions have prevented the accumulation of adequate series of patients in which the diagnosis has been confirmed by autopsy after careful clinical study. More work of this kind is necessary but enough information is available to make possible an anatomical diagnosis before death in most instances.

Often an incomplete diagnosis is of considerable value and in most cases an incomplete anatomical diagnosis together with a careful functional evaluation of the patient will make possible more accurate prognosis and intelligent treatment than will an accurate anatomical diagnosis alone.

Interventricular septal defect may be mentioned as an example of the value of an incomplete anatomical diagnosis. If cyanosis occurs in conjunction with findings of such a lesion it is often impossible to determine whether cyanosis occurs because of the large size of the defect or because it is accompanied by some other lesion such as transposition of the aorta. While the diagnosis must remain incomplete, this need not cause confusion in the prognosis. There is every reason to believe that the degree of the cyanosis, the size of the heart and the severity of symptoms will determine the prognosis and guide the management of the patient under these circumstances in the absence of exact

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\* From the Departments of Medicine and Pediatrics, University of Chicago. This work was supported in part by the Kenneth G. Smith Foundation.

† Associate Professor of Medicine, University of Chicago School of Medicine.

‡ Assistant Professor of Pediatrics, University of Chicago School of Medicine (Now Captain, Medical Corps, Army of the United States.)

knowledge regarding the minutiae of the lesion. The incidence of subacute bacterial endocarditis is about the same for both types of lesion. Exact identification of the lesion would not facilitate management of the patient in this case.

### DIAGNOSIS

The diagnostic outline published in the "Criteria for Classification and Diagnosis of Heart Disease,"<sup>1</sup> which involves the description of each case according to etiology, anatomical lesions, physiological abnormalities and functional capacity, is as useful in cases of congenital heart disease as in other types. The more complete the diagnosis, the more valuable it will be.

### ETIOLOGICAL DIAGNOSIS

During infancy the frequency of congenital lesions is so great as compared to acquired heart disease that except under unusual circumstances it is justifiable to assume that any organic disease is congenital. It follows that in the adult a definite history of abnormality extending back to infancy increases the probability that an organic lesion is congenital.

In many instances recognition of a specific lesion is the first step in diagnosis and its congenital etiology is clear because of its type.

Occasionally the diagnosis of congenital heart disease is made through exclusion, a group of atypical findings being judged to represent a congenital defect because of the lack of resemblance to any common acquired condition. This method can usually be avoided by careful study and is no more accurate than are other kinds of diagnosis by exclusion.

The differentiation of functional heart murmurs from those of congenital heart disease is frequently difficult, the problem being similar to that encountered in distinguishing between other organic disease and functional murmurs in adults but not in children. The most frequent murmur in congenital heart disease is a systolic murmur at the left of the sternum. This is also a common location for functional murmurs. The presence of a thrill, a diastolic murmur, enlargement of the heart, cyanosis, electrocardiographic abnormality or other evidence of organic heart disease gives positive indication of organic disease. The absence of such findings, however, does not indicate that a murmur is functional. The loudness of the murmur is of some help

but cannot be relied upon to differentiate the two types. The younger the patient the greater the difficulty. Functional murmurs are often relatively loud in infancy and the typical murmurs of specific congenital lesions are often late in developing so that great caution in drawing definite conclusions from equivocal findings is necessary. In infancy, for practical purposes, all murmurs are functional or indicate congenital heart disease but in spite of this differentiation is often impossible.

#### ANATOMICAL DIAGNOSIS

Thorough and extensive pathological study forms the only sound basis for anatomical diagnosis. Abbott's<sup>2</sup> classification of 1000 cases is a classical contribution in this field and is invaluable as a reference source. The relative frequency of different types of congenital lesions varies considerably in other series, however, and this series must not be given too much weight because of its size in estimating frequency. The group is derived from many sources, including some individually reported cases, and may not represent a random sample of congenital heart lesions. The series of Gibson and Clifton,<sup>3</sup> composed of 105 autopsied cases from one hospital, is in sharp contrast to the Abbott series in some respects. For example, 34 per cent of the latter group had permanent cyanosis but only 2 per cent of the former showed this complication. This is a much greater disparity than would be expected on the basis of chance. While caution is necessary in drawing conclusions from autopsy series regarding the frequency of occurrence of various lesions in clinical practice, they are of course indispensable in establishing the significance of physical signs.

#### Classification

The great number of congenital lesions (there are eighty-seven included in the Abbott table), together with the fact that there is a strong tendency for lesions to occur in combination, has made it difficult to group patients from a clinical standpoint. The classifications of White<sup>4</sup> and Dry<sup>5</sup> and Brown<sup>6</sup> are notable efforts in simplifying complex pathological knowledge to make it useful clinically. However, any classification which includes all types of congenital lesions, whether anatomical, embryological or clinical, must be complicated.

A classification according to the obvious clinical sign which

attracts attention to the fact that an abnormality of the heart exists is definitely inferior to others in the systematic study of congenital heart disease from a scientific point of view but it is justified because it systematizes the clinical approach to the diagnostic problem. In classifying patients during diagnosis it is helpful for the physician to emphasize findings that are demonstrable in the living patient rather than anatomical lesions or embryological origins of lesions, even though his aim is to make a diagnosis that is as accurate as possible anatomically. The classification given below simplifies the reasoning involved in diagnosis and frequently makes possible greater accuracy in the final diagnosis than efforts to fit clinical observation to an anatomical classification directly.

#### CLASSIFICATION OF PATIENTS WITH CONGENITAL HEART DISEASE ACCORDING TO COMMON PHYSICAL SIGNS

- 1 Patients with a systolic murmur heard at the left sternal border
- 2 Patients with cyanosis
- 3 Patients with the continuous murmur of patent ductus arteriosus
- 4 Patients with arterial hypertension
- 5 Other patients with congenital heart disease

To make such a classification complete the final miscellaneous group is necessary. The great majority of clinically important cases fall in the first four groups, however, and the simplicity and utility of the classification from a practical standpoint justify this short form, although it is recognized that many subdivisions of group five exist.

##### 1 Patients with a Systolic Murmur Heard at the Left Sternal Border

This group includes nearly half of clinically recognizable congenital heart disease. It can, to some extent, be subdivided on the basis of the location of the murmur. The murmur of *patent interventricular septal defect* is best heard in the third left interspace in most cases, while *pulmonary stenosis* is characterized by a murmur in the second left interspace, and the murmur of *patent ductus arteriosus* is best heard in the first interspace in most cases. *Transposition of the great vessels* is a common complicating defect but does not alter the location of the murmur. Differentiation on the basis of localization of the murmur is uncertain, however, deviation from characteristic locations being

common In infancy and childhood these murmurs tend to be localized at a lower level and are often heard as far down as the fourth or fifth interspace

All of these murmurs are frequently accompanied by thrills, so that the presence of a thrill does not help in differentiation between these lesions, but its location does The characteristic localization of the thrill in these lesions is the same as that of the murmurs The point of maximum intensity of the thrill is somewhat more reliable diagnostically than the point where the murmur is loudest The presence of a thrill helps to distinguish the murmurs of this group of congenital lesions from functional and other rare congenital murmurs The direction of transmission is characteristic, the murmurs of pulmonary stenosis and patent ductus arteriosus being transmitted toward the left shoulder, the murmur of transposition of the aorta to the neck and the murmur of interventricular septal defect toward the apex

Under the heading of etiological diagnosis the difficulty in differentiating systolic murmurs of congenital and functional origin has been stressed This difficulty is frequently encountered in distinguishing specific lesions as well. Murmurs and thrills may appear and become prominent after a few weeks when the physical signs have been normal at birth and murmurs that have been easily heard soon after birth may disappear entirely It is not justifiable to make a diagnosis of a specific lesion from the finding of a systolic murmur without supporting evidence in the first weeks of life On the other hand, it is impossible to be sure that such a systolic murmur is functional in early infancy

Any of the lesions in this group cause enlargement of the right ventricle apparent on physical or roentgenologic examination Enlargement of the right ventricle without enlargement of the pulmonary conus suggests pulmonary stenosis All of this group of lesions may cause right axis deviation of the electrocardiogram Defects of intraventricular conduction suggest a septal defect but normal QRS complexes are not evidence of an intact septum In general the roentgenogram and electrocardiogram are more helpful in judging the severity of lesions in this group and in separating these from other lesions than in distinguishing between them The absence of right ventricular enlargement in the roentgenogram and right axis deviation in the electrocardiogram does not indicate that a systolic murmur



is functional rather than of congenital origin but it does usually indicate that the lesion is not of great severity. Fluoroscopic examination with rotation of the patient during examination is much more valuable than is the standard chest film.

These laboratory examinations are less valuable in infants and small children than in adults. Satisfactory roentgenograms are more difficult to obtain because of poor cooperation. Even in satisfactory films the wide mediastinum and rounded globular heart of infancy show little resemblance to the cardiac silhouette in the adult. Abnormalities of chamber contour are hard to recognize and the shape often changes from one picture to another, the changes being related to respiration or crying. Angiocardiography will doubtless be of value in some cases, but is not at present completely established. This method has been the subject of a recent review by Sussman, Grishman and Steinberg.<sup>1</sup> The electrocardiogram in infancy is also more variable and of less value than in the adult.

In a considerable proportion of the patients in this group the detection of individual lesions is impossible. The confusion is made worse by the frequency with which lesions within the group occur in combination. Fortunately the inaccuracy that results from failure to distinguish between a patent interventricular septum and the same lesion in combination with partial transposition of the aorta, for example, is of very little practical significance. A large septal defect reduces cardiac reserve more than less severe combined lesions. The total reduction of efficiency is more important than the cause of the reduction. The incidence of subacute bacterial endocarditis is about the same in all lesions of this group. The susceptibility of the patients to other infections is dependent on the degree and direction of the shunt rather than upon its cause. When this group of lesions is differentiated from other conditions causing a systolic murmur in this location, the gain is small from more precise anatomical diagnosis.

## 2 Patients with Cyanosis

There is considerable overlapping between this and the preceding group and often the diagnosis of a specific lesion can be made in a cyanotic patient by the same methods indicated for Group 1. Most of the lesions with cyanosis are characterized by

a *shunt* which allows the passage of blood from the right to the left side of the heart. This may occur from defects in the auricular or ventricular septa or because of communications between the aorta and pulmonary arteries. Permanent cyanosis does not occur in these cases unless the shunt is large enough to permit mixing of the blood from the right and left sides of the heart. Normally the pressure on the left side of the heart is higher than on the right so that with small shunts the blood passes from left to right without causing cyanosis. In the presence of small shunts, however, right heart failure may reverse the pressure relationships and the direction of flow through the shunt and give rise to terminal or temporary cyanosis. Transposition of the great vessels may also give rise to cyanosis because some of the blood by-passes the pulmonary circulation. In a few instances cyanosis occurs in the absence of a shunt because of high-grade obstruction to the flow of blood, usually from pulmonary stenosis. These obstructive lesions may also occur with shunts.

A given lesion may occur in Group 1 or Group 2 or in both depending on its severity, for example, a small interventricular septal defect may cause a loud murmur but no cyanosis, if it is larger a murmur with cyanosis results, while in the case of very large defects, no murmur but pronounced cyanosis is common. This relationship between the murmur and cyanosis is not of great diagnostic help in this connection, however, because of the frequent combination of lesions. As might be expected, severe and complicated lesions are more frequent in the group with cyanosis than in the acyanotic group.

As might also be expected, permanent cyanosis is more common in the younger age groups. Since these lesions are in general more severe, the hazard is greater and many of this group die at an early age. Only a few deeply cyanotic children live to the age of twenty.

From the standpoint of anatomical diagnosis this group is important because it is composed almost entirely of cases with lesions causing large shunts and combined, complicated lesions. Exact anatomical diagnosis is frequently impossible in this group but recognition of the common significance of cyanosis makes possible intelligent management of the patient.

### 3 Patients with the Continuous Murmur of Patent Ductus Arteriosus

The classical murmur of patent ductus arteriosus is best heard in the first left interspace and it persists through all of systole and part or all of diastole. It is transmitted toward the left shoulder. If the patency is large, enlargement of the pulmonary artery is demonstrable by roentgenographic examination and peripheral signs resulting from the high pulse pressure are apparent. The peripheral signs are identical with those of aortic insufficiency, but the location and type of the murmur together with the enlargement of the pulmonary artery differentiate this lesion from aortic lesions.

It is very important that this lesion be recognized. It is relatively common, the open ductus is a frequent site of bacterial endocarditis and often causes heart failure, and it has been closed successfully by surgery in a number of instances.

Unfortunately, pathological studies have shown that patent ductus arteriosus may occur in the absence of the typical, easily recognized murmur. Some cases, especially in children, have caused only a systolic murmur and some have been found when no murmur at all has been noted. The other signs may help in detecting some of these cases but many will continue to be missed until new diagnostic methods are available.

### 4 Patients with Arterial Hypertension

*Coarctation of the aorta*, which is the congenital lesion which causes hypertension, can be recognized easily by the fact that the arterial pressure is higher in the arms than in the legs and by the fact that notching of the lower edges of the ribs is apparent on chest roentgenogram because of the enlargement of the intercostal arteries which are the principal collateral channels around the lesion. This roentgenographic sign is not as clear-cut in children as in adults. Failure to make the diagnosis of this lesion occurs because of failure to think of it as a possibility rather than from difficulty of diagnosis. Small degrees of coarctation which do not cause elevation of blood pressure in the upper extremities are not important clinically.

### 5 Other Patients with Congenital Heart Disease

This group will not be discussed at length because it is composed of lesions which are rare or in which diagnostic methods are unreliable or unsatisfactory. The great majority of clin-

ically important lesions are included in the first four groups. Defects of the interauricular septum, bicuspid valves, supernumerary valve leaflets, anomalous chordae and so forth give rise to no signs or to signs that are irregular and inconsistent and therefore an ante-mortem diagnosis is not made. A few lesions such as aortic stenosis and pulmonary insufficiency are rare but are rather easy to recognize. Some lesions such as anomalies of the aortic arch are usually found on roentgenographic examination. The clinical diagnosis of these uncommon lesions is sometimes possible, but they are encountered but rarely in practice and too much concentration on the rare clinical patterns is likely to do more harm than good because of the inevitable confusion that results.

#### PHYSIOLOGICAL DIAGNOSIS AND FUNCTIONAL EVALUATION

The one most important feature of physiological diagnosis that occurs in congenital heart disease alone is the estimation of the size and direction of shunts. Quantitative methods are not in general use. Generalities are unsafe, but usually the presence of cyanosis indicates a shunt of some magnitude from right to left. If a shunt is recognizable the degree of enlargement of the chamber receiving the blood gives some clue to its size.

The symptoms and signs of cardiac insufficiency, the arrhythmias and so forth have approximately the same significance as in acquired heart disease.

The methods used and the significance of functional evaluation are the same as in acquired heart disease. Physiological diagnosis and functional evaluation of the patient should be stressed in connection with congenital heart disease. They are frequently neglected because of the difficulty of anatomical diagnosis.

#### PROGNOSIS

The fact that patients with severe congenital heart lesions occasionally survive to great age does not indicate that prognosis is entirely impossible. Approximately the same degree of accuracy is possible as in other types of heart disease. The uncertainty that exists in regard to the development of subacute bacterial endocarditis is quite similar to the uncertainty regarding the recurrence of myocardial infarction. In each case the possibility of disaster can be foreseen but its likelihood is not sufficiently great to justify pessimism on the part of the patient.

As in severe rheumatic heart disease it is frequently possible to predict that the cardiac reserve will remain very low, but in neither case is it possible to predict the time of death with great accuracy. Too many unpredictable hazards are involved to estimate when any particular heart will become unable to support life.

In general in adults deterioration of cardiac functional capacity is slower in patients with congenital heart disease because the lesion itself is not progressive. The cardiac reserve can be estimated from the symptoms of heart failure which the patients experience. The prognosis for continuation of life may be improved if the patient's mode of life can be modified so that he avoids symptoms. Symptoms or signs of heart failure, cyanosis, and enlargement of the heart make for a bad prognosis. The intensity of these signs is important. Occasionally a person with deep cyanosis lives for many years, but he will be very unlikely to do so if his heart is big and he has heart failure. Occasionally a person with a very large heart lives for many years, but such a development is unlikely in the presence of cyanosis or heart failure. Throughout adult life the prognosis of congenital heart disease patients from the standpoint of cardiac function depends more upon these factors than upon the anatomical lesion.

Intercurrent infections have been a common cause of death in these patients. In general the susceptibility to such infections and their mortality rates are proportional to the reduction of functional capacity of the circulation. The large number of deaths from this cause may be somewhat reduced in the future as chemotherapy becomes more successful.

Subacute bacterial endocarditis is a serious hazard to some of these patients. Its frequency is high in cases with valve lesions and with interventricular shunts and arteriovenous shunts. It is very uncommon in interauricular septal defects. It is particularly frequent in patients with patent ductus arteriosus.

Prognosis is exceptionally difficult in early infancy. Many unpredictable deaths occur in the first year of life but on the other hand some patients with severe cyanosis at birth do surprisingly well. After the first year minor signs may disappear, but in general severely involved hearts do not improve. Those patients who have heart failure or marked enlargement of the heart in early childhood rarely live to be adults. Most of the

cyanotic patients do not survive the period of growth. The few that do are almost always free of symptoms of heart failure and have relatively small hearts.

### TREATMENT

The treatment of congenital heart disease differs little from other forms of heart disease. Control of activity to avoid deterioration of functional capacity is important. There is no indication for more restriction than is necessary to avoid heart failure, however, and a careful, continuous study of each patient is essential in order to guide activity properly.

Protection of the patients against infection is important, especially in childhood. Every infectious disease is a major hazard and must be treated as a very serious complication regardless of how insignificant it appears at the outset.

Patent ductus arteriosus has been corrected many times surgically. The operative mortality is not excessive in experienced hands. An attempt should be made to ligate a patent ductus in every case which shows serious functional impairment and in cases in which subacute bacterial endocarditis is present. Several cases of subacute bacterial endocarditis which have been cured by ligation of a patent ductus arteriosus are on record. Ligation of every patent ductus arteriosus may be desirable, but more experience with the operation and a better knowledge of the operative mortality should be available before such treatment is recommended.

### SUMMARY

Most cases of congenital heart disease may be placed in one of four groups corresponding to a single prominent, easily recognizable physical sign.

1 Cases with a systolic murmur at the left border of the sternum. This group includes cases with one or more of the following lesions: Interventricular septal defect, pulmonary stenosis, transposition of the great vessels and a few other rare anatomical lesions. The prognosis and management of cases within this group is more closely related to the degree of physiological disturbance than to the specific anatomical lesion.

2 Cases with cyanosis. This group includes cases with large shunts from the right to left side of the heart, cases with smaller shunts and right heart failure, and a few other severe lesions. In general the prognosis is poor in these cases. The few cases which

do well have little enlargement of the heart and few symptoms of lowered cardiac reserve.

3 Cases with the continuous murmur of patent ductus arteriosus

4 Cases with arterial hypertension in the arms but not in the legs These patients have coarctation of the aorta

This simple grouping includes the most common lesions Other lesions are uncommon or not recognizable before death

In infancy the diagnosis and prognosis of congenital heart disease is much less satisfactory than in older children and adults The greater severity and complexity of lesions, the inconstancy of physical signs, and the greater difficulty of physical and laboratory examination all increase the difficulty

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## THE SIGNIFICANCE OF GASTRO INTESTINAL TRACT ABNORMALITIES AS RELATED TO THE MANAGEMENT OF CARDIAC DISORDERS\*

CLARENCE F G BROWN M.D.,† and RALPH E. DOLKART M.D.‡

PRIOR to Herrick's recognition of coronary occlusion as a disease entity, and prior to the availability of the electrocardiogram as an adjunct in diagnosis, "acute indigestion" was an acceptable cause of death. Although we now use the term coronary occlusion, the tendency for occurrence following over-eating is still an accepted phenomenon. In recent years an ever-increasing emphasis is being placed upon the interrelationship between reflex phenomena involving the cardiovascular and gastro-intestinal systems.

### CHRONIC GALLBLADDER DISEASE

Willius and Fitzpatrick<sup>1</sup> almost twenty years ago reported that 39 per cent of patients with chronic gallbladder disease had associated changes of the cardiovascular system, coronary artery sclerosis being the most common in occurrence. More recently Ravdin and his co-workers have attached considerable importance to these concomitantly occurring disease entities and recommend cholecystectomy in patients who have symptoms of angina and in whom pathologic gallbladders can be demonstrated. Although Maisel and Alvarez<sup>2</sup> report that there is no proof that biliary tract disease has any direct influence in the production of heart disease, in our opinion the clinical problem does not revolve around the presence or absence of such a relationship. Rather, if the presence of gallbladder disease acts as a reflex trigger mechanism through which the frequency of anginal attacks is increased, then removal of the associated ab-

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\* From the Medical Departments of Northwestern University Medical School and St. Luke's Hospital.

† Assistant Professor of Medicine, Northwestern University Medical School. Senior Attending Physician, St. Luke's Hospital.

‡ Instructor in Medicine, Northwestern University Medical School. Assistant Attending Physician, St. Luke's Hospital.



normality, the gallbladder, is a constructive step in therapy. Studies by Woollard, Ankep and Stacey, Mann, Wiggers, and others would seem to indicate that the coronary arteries are dilated by sympathetic impulses of adrenalin, and constricted by the vagus.<sup>3</sup> It is probably through mediation with such reflex connections that gallbladder abnormalities alter the course of individuals with coronary artery disease.

From a clinical point of view, careful study and search for gallbladder disease should be made in the case of individuals who manifest food intolerances, have associated stomach or bowel distress as indicated by gaseous distention after meals, or upper right quadrant distress, together with evidence of coronary artery disease. Not uncommonly, there may be variations from the usual sites of pain radiation or pain reference of both cardiac and gallbladder origin. Surgical removal of the gallbladder in properly selected risks is definitely indicated not only in our own experience but in the cumulative case reports in the literature.

Individuals who are not proper surgical risks should be managed with care and caution with a view toward minimizing the reflex stimuli arising from the gallbladder. These principles we have previously discussed.<sup>4,5</sup> Briefly they entail consistent use of antispasmodic drugs, preferably tincture of belladonna or atropine up to the point of atropinization consistent with the patient's welfare and comfort, dietary control, use of a frequent-feeding bland diet, of low-caloric content with an obese patient, avoidance of cooked fats but use of uncooked fats within limits of fat tolerance as discussed by Ivy, use of oxidized bile salts, again dependent upon the patient's tolerance. Frequent feedings may still be achieved in obese patients through the use of gelatin feedings between meals instead of foods with higher caloric content.

#### HIATUS HERNIA

Hiatus hernia is a second category in which there is considerable interrelationship between the cardiac and gastro-intestinal systems. Not infrequently substernal pain radiating to the shoulder may be a presenting symptom of hiatus hernia which is commonly misinterpreted as of coronary artery origin. Exertional dyspnea may be present but may result from reduction of vital capacity due to the presence of a large amount of the stomach in the chest. Other cardiac symptoms may be the result of rota-

tion or displacement of the heart or from increased intra-abdominal pressure from below. The foregoing indicate the mechanical aspects of hiatus hernia which may mimic heart disease. Both conditions may occur together and in such instances there is no doubt a reflex trigger mechanism as in gallbladder disease which accentuates the frequency or degree of coronary artery spasm. Treatment of hiatus hernia is largely in either of two categories—surgical repair or palliative. Small frequent feedings, careful observance of an upright posture during and considerably after the ingestion of food, and use of antispasmodics.

It is interesting to note that more frequently symptoms from a hiatus hernia develop in later life. The age incidence of the group reported by Murphy and Hoy<sup>a</sup> was in the third decade of life or beyond. It is our impression that the occurrence of symptoms in later years even though the abnormality probably existed for a considerable period of years, if not at birth, may be explained by reduction in threshold levels for visceral stimuli or because of increased changes in the blood vessels themselves.

#### IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome or nervous indigestion is by far one of the commonest gastro-intestinal tract abnormalities. It is our opinion that almost any intra-abdominal viscus may initiate reflexes which may affect the coronary circulation, heart rate or rhythm. It is well established that actual torsion or simple tension from any cause which twists or pulls a viscus sets up visceral reflexes which affect the entire circulatory system.

In searching for causes of coronary embarrassment, the abdominal organs classed as the hollow visci are the more frequent offenders. Emptying an over-full urinary bladder many times relieves a dull precordial discomfort. In a spastic bowel, relief of chest pain is often achieved by a redistribution of the gases or by a bowel movement with free expulsion of gas and resultant lowering of the intraluminal pressure thresholds. All of these phenomena are increased by the presence of organic changes in the wall of the intestine. In diverticulosis increased production of reflex stimulation may result when there is mechanical embarrassment in one or more of the diverticula which is further increased when an actual diverticulitis is present with actual inflammation and concomitant colon spasm wherever it occurs.

Gilbert, Fenn, and LeRoy<sup>7</sup> as well as others have demonstrated definite vasoconstriction of the coronary arteries upon distention of an inflated balloon in the stomach. Distention of the free abdominal cavity with air also caused constriction of the coronary arteries, which did not occur if the vagi had been cut or if atropine had been administered. They believe the latter phenomenon is an explanation of the relief of an anginal attack occurring in a patient whose abdomen is distended with gas, by the passage of flatus or belching.

It is equally interesting to correlate the high incidence of all types of sudden vascular accidents with either the desire to defecate or during or immediately after the bowel movement. This formerly was considered to be "straining at stool," but as many occur with just the urge to defecate and happen while the patient is on his way to the toilet. In this connection one of us has recently seen a patient hospitalized for a cataract extraction who had a coronary occlusion on his tenth postoperative day following the administration of a large saline purgative. Possibly with any radical change of intraluminal pressure thresholds of the hollow visci there is a general vascular repercussion and readjustment which brings out defects in the coronary arteries or any portion of the cardiovascular system. Careful observance of physiologic principles of bowel management obviously is indicated. It cannot be stressed too strongly that functional disorders should be evaluated and treated inasmuch as they predominate in bringing out the early pathologic manifestations via the route of visceral reflexes.

#### RAPID ENLARGEMENT OF LIVER WITH RIGHT HEART FAILURE

The last entity we should like to consider is one we have previously mentioned<sup>8</sup> and which Boyer and White<sup>9</sup> have recently discussed, namely rapid enlargement of the liver associated with right heart failure. This is well borne out in individuals with a marked kyphoscoliosis with heart failure due to chest deformity and reduction in vital capacity. Right heart failure occurs in the great majority of these individuals, and right upper quadrant pain is one of the earliest symptoms. Apparently enlargement of the liver with distention of Glisson's capsule produces a sensation of fullness and pressure in the abdomen and frequently with severe and intense right upper quad-

rant pain Kuntz believes that pulling down on the attachment to the diaphragm is also an important mechanism

### SUMMARY

The interrelationship of reflex phenomena between the abdominal viscera and the cardiovascular system have been indicated. Therapeutic efforts must be directed toward physiologic control of the gastro-intestinal as well as the cardiovascular systems

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## DISSECTING ANEURYSM OF THE AORTA\*

EMMET B. BAY, M.D.†

DISSECTING aneurysm of the aorta rivals syphilis in the number and variety of other disease entities which it may simulate and with which it may be confused. In the large and growing literature‡ on the subject it is apparent that it is most often misdiagnosed coronary thrombosis. It has also been mistaken for syphilitic aortitis, cerebral vascular accidents, mediastinal tumors, pneumonia, diaphragmatic hernia, cholelithiasis, pancreatitis, nephrolithiasis, ruptured peptic ulcer, mesenteric thrombosis, embolic occlusion of the arteries in the extremities and disease of the lower spinal cord.

The incidence of dissecting aneurysm in general is not available but though low, it appears to be large enough to warrant inclusion in the thinking of a physician attempting the diagnosis of an acute, severe chest or back pain in an older patient. As a cause of sudden death, Mote and Carr<sup>1</sup> found it in about 11 per cent of nontraumatic coroner's cases. The number of cases correctly diagnosed ante mortem is increasing rapidly and represents from 10 to 30 per cent of most of the series reported.

### PRECIPITATING FACTORS

It occurs much more frequently in men than in women and usually in patients with *pre-existing hypertension*. Syphilis of the aorta is not an important predisposing factor nor is external trauma as frequent a precipitating factor as was formerly thought.

The role of *unusual exertion* in its onset is not yet a settled point. Cherry and Cherry<sup>2</sup> believe that on a statistical basis exer-

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\* From the Department of Medicine, University of Chicago School of Medicine.

† Professor of Medicine, University of Chicago School of Medicine.

‡ No attempt is made to be all-inclusive in the appended bibliography. For an excellent historical account of our knowledge of this disease and a good bibliography the reader is referred to an article by Flaxman in the *American Heart Journal*, 24:654, 1942.

tion is a coincidental rather than a necessary precipitating factor. This, of course, has important medicolegal connotations. There are case histories available, however, which suggest strongly that, in the presence of a background for trouble, excessive exertion is dramatically related to the beginning of symptoms.

#### ETIOLOGY AND PATHOLOGY

The pathogenesis probably includes two main modes of development. Erdheim's<sup>3</sup> medial necrosis is the primary lesion in some cases and results in dissection by virtue of hematoma formation within the wall of the aorta brought about by rupture of the vasa vasorum. This subsequently may break through the intima in one or more places.

Primary rupture of the intima and subsequent dissection of the media also occur in the absence of pre-existing medial necrosis. Such intimal tears may occur without dissection and have been labeled incomplete rupture of the aorta by Gallavardin and Gravier<sup>4</sup> and Peery.<sup>5</sup> The latter states that this lesion is probably more frequent than dissecting aneurysm although it has not so far been diagnosed ante mortem.

Secondary pathologic changes serve to explain many of the mistakes in ante-mortem diagnoses, as was pointed out by Crowell.<sup>6</sup> The intimal tear, with or without medial necrosis, may occur at any point along the aorta but more often is found in the ascending aorta near the aortic ring and frequently in that portion of the wall within the reflected pericardial sac. The subsequent dissection may travel in either or both directions up and down the aorta as well as around it. Its encroachment on the branches of the aorta and on the aortic ring produces the varied symptomatology which at once makes its diagnosis possible in an increasing number of cases and serves to confuse it with the wide range of clinical entities cited above. It may, for example, result in a suddenly developing aortic insufficiency by one of three mechanisms described in the literature. It may result in the partial or complete occlusion of one or more coronary, subclavian, carotid, intercostal, renal, mesenteric or common iliac arteries. The vessel or vessels involved determine the signs and symptoms produced.

Death may come suddenly when the dissecting aneurysm or the incomplete rupture of the aorta breaks through the adventitia. There are cases on record, however, in which survival of

such an accident has occurred, at least for a few days. The rupture may occur into the pericardial sac with resulting cardiac tamponade or into the pleural space, the mediastinum, the abdominal cavity, the retroperitoneal tissues, or even into the gastro-intestinal tract and be accompanied by the vomiting of blood

## DIAGNOSIS

**SYMPTOMS**—Although "silent" dissections of the wall of the aorta are thought to occur, by far the majority of those which result in survival are accompanied by *pain*. This pain is often excruciating, unrelieved by large doses of morphine. It frequently resembles the distress in the chest produced by coronary thrombosis but does not radiate to the arms characteristically. It does tend to radiate to the back between the scapulae and sometimes to the neck and head, lower back and legs. Occasionally it travels, hour by hour or day by day, down the back from the neck to the legs. It may be throbbing in character and intermittent, lasting a few hours at a time.

Other symptoms, not invariably present, include dyspnea, vomiting, loss of consciousness, transient paralysis of the legs and in some instances those of heart failure. Rarely, hematuria has been prominent enough to suggest primary renal pathology.<sup>7</sup>

**PHYSICAL FINDINGS**—On physical examination there may be little to find which differs from the pre-existing record when such is available. The *blood pressure*, usually elevated previously, does not drop unless the patient develops the signs and symptoms of shock or unless the orifice or first portion of the artery in the extremity tested has been involved in the dissection. In the latter instance, the drop in blood pressure in one or two extremities and not in the others, in the presence of chest and back pain, points the way to a correct diagnosis.

The sudden development of the *diastolic murmur of aortic insufficiency* accompanied by the increased pulse pressure and other peripheral manifestations of this lesion within a day or two after the onset of chest and back pain is another clue strongly suggestive of the true nature of the pathology present when it occurs.

Transient changes in the strength and reflexes of one or both lower extremities when other symptoms of a dissecting aneurysm exist help to make the diagnosis definite.<sup>8</sup>

In those instances in which the patient lives for months or years after the onset, there may be remarkably little to show for it on physical examination or the signs of gradually developing heart failure may supervene

**X-RAY STUDY**—Among the laboratory procedures, roentgenography and fluoroscopy of the chest are the most helpful. A generalized widening of the aorta, especially in oblique views, is the characteristic finding. Occasionally this may include a widening of the vessels of the upper mediastinum

**ELECTROCARDIOGRAPHY**—The electrocardiogram usually does not change materially unless the coronary orifices are involved in the dissection. This negative finding is of some help in the differential diagnosis. In the event the coronaries are obstructed the electrocardiogram may follow the patterns of myocardial ischemia seen in coronary thrombosis and is likely to lead to a mistaken diagnosis unless some of the other main branches of the aorta are similarly affected in a way which reveals that the primary difficulty is in the aorta rather than in the coronary arteries

**TESTS FOR SYPHILIS**—The Wassermann reaction and other serological tests for syphilis when positive likewise serve more often than not to confuse the diagnosis. This is especially true when the dissection results in the development of aortic insufficiency.<sup>9</sup> When it can be ascertained to be the case, the sudden onset of the latter helps to distinguish between luetic aortitis and dissecting aneurysm involving the aortic ring

### PROGNOSIS

The course of this disorder varies from sudden death at the onset to more or less asymptomatic survival for several years in a few instances. It is probable that, as in the case of coronary thrombosis, prognoses will become somewhat more favorable as diagnoses improve. It will always have to be regarded as a serious accident to the cardiovascular system

### TREATMENT

The treatment consists in rest in bed during the acute stage, with whatever sedation proves necessary to keep the patient as comfortable as may be. Repeated doses of morphine are frequently indicated but the smallest amount should be used which will suffice to relieve the pain.



Perhaps the most important feature of the treatment rests in making a diagnosis which will preclude surgical interference for various supposed colics or arterial emboli

#### PRESENTATION OF CASES

With these considerations in mind the seven cases found at autopsy at the University of Chicago Clinics during the first fifteen years of operation were reviewed. Only two of these cases were correctly diagnosed during life. In the presentation of these cases, special attention will be given to findings in the histories which might have led to a correct diagnosis in those instances in which it was missed.

**CASE I**—The patient was a white man seventy-three years old in April of 1929 when he was first seen. He had a history of herpes zoster involving the left leg in September, 1928, at which time diabetes was also diagnosed. He complained of residual pain in this leg. Nothing was found on examination germane to this discussion except a blood pressure of 170/90. Two years later he was seen again complaining of intermittent claudication and no pulse could be found in either dorsalis pedis or posterior tibial artery. Two months later he complained of mild pain in the arms and back. Three months later (August 31, 1931) he entered the hospital complaining of substernal pain of eight hours' duration and radiating down both arms. The findings were essentially unchanged except for the blood pressure, which was 150/98. Three days later a pericardial friction rub was heard and the blood pressure was 110/70. Electrocardiograms were typical of coronary thrombosis and this diagnosis was made. The patient died suddenly six days later.

*Autopsy* revealed 270 cc of blood in the partially obliterated pericardial sac. There was an occlusion of the circumflex branch of the left coronary artery and a myocardial infarct which had ruptured. An incidental finding was a very small (1 by 3 cm) dissecting aneurysm 5 cm above the bifurcation of the aorta. The material in this aneurysm included necrotic debris as well as discolored blood and it was presumed to be old.

*Comment*—The cause of death was properly diagnosed in this case but there was an additional finding—the small dissecting aneurysm near the end of the aorta, which appeared much older. Even if the assumption be made that it was somehow concerned in the production of his leg pains it is extremely doubtful that a correct diagnosis could have been made. There was no history

of low back pain of any severity and there were ample reasons for leg pain in the shape of arteriosclerosis and a history of herpes zoster

**CASE II**—This white man of sixty-eight had a history of anginal pain radiating to the right arm for one year before he was first seen on June 26, 1931. His heart was slightly enlarged and his blood pressure was 145/96. Electrocardiogram revealed what we would now call "left ventricular strain." Roentgenography and fluoroscopy showed a dilated, tortuous senile aorta with calcified plaques in the knob. There was some doubt as to whether the first portion of the aorta was sufficiently dilated to warrant the diagnosis of aneurysm, and the roentgenologist who first raised the question decided against it at a later visit. He had two attacks of precordial pain, dyspnea and cyanosis lasting for hours, one on July 25, 1931, and one September 15, 1933. These were diagnosed as coronary occlusions. After the last one he had symptoms of heart failure until his death March 19, 1934.

*Autopsy* revealed a generalized arteriosclerosis with marked calcification and narrowing of both coronary arteries. There was disseminated and focal fibrous scarring of the myocardium with beginning aneurysmal dilatation of the apex of the left ventricle (probably small healed infarcts). There was general dilatation of the ascending aorta and medial necrosis and rupture in the arch with the formation of two small dissecting aneurysms (one 1.5 cm., the other 8 mm. in its longest diameter). These small aneurysms were filled with laminated organizing blood clots.

*Comment*—Again the cause of death was properly diagnosed but the existence of incomplete rupture of the aorta with small dissecting aneurysms was unsuspected during life. It is possible that one or two of his attacks of anginal pain differed in character or radiation sufficiently to make the alert physician suspect some such episode but this does not seem at all likely. On a statistical basis multiple sites for the origin of variable coronary pain would be much more probable.

**CASE III**—The patient, a white man aged fifty-one years, was first seen August 26, 1932, complaining of dizziness, especially when stooping. His blood pressure was 188/128 and the aortic second sound was ringing although he was said to have had a normal blood pressure two years previously. Cardiac and renal functions were within normal limits at this time. He had no other symptoms until March 23, 1934, when he noticed an occasional desire to sit up in

bed to breathe freely. By January of 1935 he had frank symptoms of myocardial insufficiency. He entered the hospital March 8, 1935, complaining of dyspnea, weakness, cough and frontal headaches. His blood pressure was 224/184 and the pulse rate was 120 per minute. The heart was only slightly enlarged to percussion and a systolic murmur was heard both at the apex and base. He was markedly orthopneic. There was a definite pulsation in the epigastrium synchronous with the heart beat. Kidney function was now reduced by the urea clearance test to about 50 per cent of normal. On his last day of life, March 15, 1935, he failed rapidly and the blood pressure gradually dropped to 92/70 just before death. The clinical diagnosis was malignant hypertension with myocardial and renal insufficiency.

*Autopsy* revealed arteriolar nephrosclerosis with marked cardiac hypertrophy and marked atheromatosis of the large and medium sized arteries. There was an early bronchopneumonia. The abdominal aorta had more atheromatosis than the thoracic aorta and contained an occasional fibrous patch. Microscopically there was one early thrombus in the media of the abdominal aorta in an area representing the beginning formation of a dissecting aneurysm.

*Comment*—The anatomic diagnosis confirmed the clinical diagnosis of malignant hypertension. Although the microscopic findings permitted the pathological diagnosis of early dissecting aneurysm the presumption is high that this lesion was terminal and asymptomatic and hence not capable of diagnosis during life.

**CASE IV**—This patient was a forty-three-year-old white man who was first seen on July 2, 1935, complaining of "kidney trouble." Three years previously he had had swelling of the eyelids and ankles diagnosed nephritis elsewhere. For six months he had noted an increasing shortness of breath. Off and on during the three years he had had a pain in the back of the neck, pounding in character and synchronous with the heart beat. Examination revealed a pale, dyspneic man whose heart was enlarged and whose blood pressure was 215/130. His hemoglobin was 50 per cent and his red blood count was 2,190,000. The urine showed albumin 4 plus, a few red blood cells and occasional hyaline and granular casts. Renal function was 10 per cent of normal.

The patient was hospitalized on July 10, 1935, and improved slightly thereafter until the evening of July 17, when he suddenly developed an excruciating pain between his shoulder blades. Five minutes later the pain radiated to the precordium and left arm. He

was more dyspneic and somewhat cyanotic. He was given  $\frac{1}{4}$  grain of morphine, repeated in twenty minutes, and two hours later  $\frac{1}{6}$  grain. His blood pressure at first was 254/148. The next day it was 224/132 at 8 00 A. M., 228/130 at 10 00 A. M., 226/128 at 12 00 M and 228/126 at 5 00 P. M. During this day he received  $\frac{3}{8}$  grain of morphine and was drowsy and partially disoriented. Without further sedation he remained completely disoriented until July 23, although his blood pressure remained between 224 and 242 systolic and between 114 and 136 diastolic. On July 23 he complained of more pain in the chest and back and was given two doses of morphine, each  $\frac{1}{4}$  grain. The next day he developed a loud pericardial friction rub. The next day, July 25, 1935, his blood pressure dropped for the first time to 152/84 and he died at 3 50 P. M. The clinical diagnosis was chronic diffuse glomerulonephritis, renal and myocardial insufficiency, and dissecting aneurysm of the thoracic aorta.

*Autopsy* revealed chronic glomerulonephritis and hypertrophy of the left ventricle of the heart. There was a transverse rupture of the aorta at the arch with an organized peri-aortic hematoma and a dissecting aneurysm arising at the point of rupture and extending distally 2 cm. There was a uremic pericarditis.

*Comment*—The correct ante-mortem diagnosis was made in this case in spite of a strong suspicion of a coronary thrombosis largely because the blood pressure failed to drop, the electrocardiogram was not characteristic of coronary occlusion and the pain started in the back between the shoulder blades. The diagnosis, made originally by an assistant resident, was the more commendable in the face of the facts that within five minutes the pain had largely shifted to the precordium and radiated down the left arm, a frank pericardial friction rub developed later and lastly, the terminal uremic disorientation made the symptomatology vague.

**CASE V**—This white man entered the hospital on July 6, 1936. That morning at 6 45 he was seized with a sharp, stabbing pain over the left cheek which radiated to the back of the neck and down the spine to about the 8th thoracic vertebra. The pain in the back persisted as the pain in the jaw subsided. Later in the day he developed "pin-pricks" in the right arm. There was no sternal or precordial pain. He had no knowledge of pre-existing trouble. On examination little was found except a blood pressure of 176/120, a white blood count of 13,200 and sugar 2 plus in the urine. That evening he suddenly stopped talking in the middle of a sentence, became unconscious and his systolic blood pressure fell to 72. The

next day his blood pressure was 110/98 and an electrocardiogram was not characteristic of coronary thrombosis. Chest roentgenograms taken on a "pneumonia bed" showed a widening of the mediastinal shadow, diagnosed as an aortic aneurysm by the roentgenologist. The blood pressure on the next day was 128/88 in the left arm and 130/90 in the right. He still had pain across the shoulders. He suddenly expired at 4 30 A. M. the next morning (July 9, 1936). The clinical diagnosis was dissecting aneurysm of the thoracic aorta.

*Autopsy* revealed a dissecting aneurysm of the aorta with aortic medianecrosis, and rupture of the aorta at the ring with hemorrhage into the pericardial sac, periaortic tissue and both pleural cavities. There was mild coronary atherosclerosis.

*Comment*—The correct clinical diagnosis was based upon the location and radiation of the pain (only in the back, never precordial), the lack of electrocardiographic change and the roentgenographic finding of widening of the aorta. The drop in blood pressure was misinterpreted as evidence of coronary thrombosis but this opinion did not prevail in the face of accumulating laboratory evidence to the contrary.

CASE VI—This patient, a white man aged sixty-eight years, entered the hospital on May 10, 1940. He had known of high blood pressure for six months. For four months he had had an increasing weakness, dyspnea and weight loss and had vomited for the first time the day before admission. On the day of admission he developed lower left chest pain of intense severity. On examination he appeared emaciated and sick. His heart was enlarged and there was a systolic apical murmur. His blood pressure was 220/148 and the heart rate was 112. One hour later there was a loud pericardial friction rub. Hemoglobin was 60 per cent, red blood count 2,880,000. The urine showed albumin 3 plus and a few hyaline casts. He was given morphine on three occasions during the first two days because of severe precordial pain and dyspnea. His blood pressure on the second day was 200/160 and on the third was 144/88. He became comatose and died on May 13, at 3 15 A. M. The clinical diagnosis was hypertensive cardiovascular disease and coronary thrombosis.

*Autopsy* revealed a chronic arteriolonephrosclerosis and chronic primary hypertension with marked concentric hypertrophy of the heart, acute serofibrinous uremic pericarditis and marked atherosclerosis of the aorta and coronary arteries. An early dissecting aneurysm was found in a microscopic section of the first portion

of the aorta. At this point there was a diffuse inflammation of the media characterized by the presence of polymorphonuclears and mononuclears as well as fibrinoid necrosis and a definite break in the intima and media.

*Comment*—In retrospect it is probable that the patient's severe precordial pain was that of uremic pericarditis and that the microscopic tear in the aorta had nothing to do with it. The mistaken clinical diagnosis of coronary thrombosis might have been avoided, too, if serial electrocardiograms had been taken. This was not done because of overconfidence on the part of the clinician in his early diagnosis and because the patient was continuously in an oxygen tent. Both of these are inadequate reasons. The dissecting aneurysm was probably too small to permit of an ante-mortem diagnosis although not enough is yet known about the degree of pain such a lesion can produce.

CASE VII—This white man of fifty-two years entered the hospital on January 29, 1942, complaining of shortness of breath and edema of the ankles of seven months' duration. A physician who saw him before admission had found a blood pressure of 240 and had put him to bed for a time. His symptoms increased in severity and included a cough and some vertigo on admission here. He had had low back pain for an indefinite but "long period" of time which had become much worse during the month preceding his admission. This pain did not radiate but was at times "very severe." On examination he was a very obese, worried patient with some orthopnea. The heart was enlarged, there were systolic and diastolic murmurs at the base and the blood pressure was 256/110. Respirations were 30 per minute. There was a pitting edema of the ankles. Albumin and casts were found in the urine. He was treated for heart failure and lost 20 kg. in nineteen days. He was discharged subjectively improved with a blood pressure which averaged 190/115.

The patient re-entered the hospital on April 27, 1942, complaining of the same symptoms, i.e., dyspnea and edema of the ankles and a cough. He had seen clotted blood in the urine on two or three occasions two weeks before this admission. He had also had frequent, severe aches in the right flank. His condition remained unchanged until May 4, 1942, when, at 3 00 A. M., he developed a pain "in the left shoulder blade" and felt "different than he had ever felt." Morphine gave temporary relief but he was found dead in bed at 1 00 P. M. His blood pressure had dropped from 200/110 to 160/95 and then returned to 200/120 on this day. The clinical

diagnosis was hypertensive cardiovascular disease with a terminal coronary occlusion.

*Autopsy* revealed a large transverse laceration of the ascending aorta just above the valve and a dissecting aneurysm extending the entire length of the aorta, into both common iliac arteries and out along the right renal artery. There was a tear through the adventitia of the ascending aorta with hemorrhagic infiltration of the mediastinal tissues and a massive, fatal hemopericardium (cardiac tamponade). Although there was marked aortic sclerosis, sections showed only a very mild medial degeneration. Embolic occlusion of a left renal branch and of a branch of the splenic artery had occurred. There was profound atrophy of the cerebral cortex.

*Comment*—The terminal event in this patient's illness might have been suspected if more attention had been paid to the location of his pain, the recovery in his blood pressure and possibly to the gross hematuria occurring two weeks before death. The latter symptom, however, might well have been the result of the embolic occlusion of the renal artery found postmortem. His great obesity (he weighed 133.4 kg [293 pounds]) and his clouded sensorium contributed to the difficulty. The one made for technically unsatisfactory chest roentgenograms, the other for doubt about the location, duration and severity of his low back, right flank and later, left scapular pain.

#### SUMMARY AND CONCLUSIONS

Some helpful leads to the making of a correct ante-mortem diagnosis of dissecting aneurysm of the aorta have been gathered from the literature. These may be epitomized by saying: When severe pain, especially upper back pain, is accompanied by cerebral symptoms, a change in the blood pressure of one extremity only, hematuria, transient paralysis of the legs, no electrocardiographic changes, a widened aorta or a suddenly developing aortic insufficiency, dissecting aneurysm should be suspected.

Seven cases found at autopsy have been reviewed. In four the diagnosis was not made and most probably could not have been made. In two the ante-mortem diagnosis was made correctly. In one the condition was not suspected when there were some hints of the type mentioned above which were overlooked.

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## A SURVEY OF RHEUMATIC FEVER IN A LARGE STATION HOSPITAL\*

CAPTAIN MARTIN H WENDKOS† and MAJOR JOHN NOLL, Jr‡  
Medical Corps, Army of the United States

BECAUSE of the average age of the military recruit it is to be expected that acute rheumatic fever would not be infrequently encountered among those in the armed forces. Unfortunately, its detection is not always easy, for as Paul<sup>1</sup> states "The concept of rheumatic fever as an entity has slowly emerged from a group of joint diseases and as a matter of fact it is still not completely free, for there are certain bonds which entangle it with the poorly understood disease—rheumatoid arthritis." He therefore takes the view, with which we thoroughly concur, that since heart disease is an integral part of the rheumatic fever picture, the recognition of active involvement of the heart in cases of acute polyarthritis should help to identify the acute rheumatic state. Unfortunately, in our experience, and in that of others,<sup>2 3, 4</sup> in adults with acute migratory polyarticular rheumatism the clinical expression of active carditis such as significant murmurs or cardiac enlargement, even when the latter is sought for with the aid of the teleoroentgenogram, has frequently been lacking. Under such circumstances it is therefore to be expected, considering the high incidence of electrocardiographic abnormalities which have been recorded in various surveys<sup>3 5 6 7, 8 9 10</sup> among patients with clinically recognizable acute rheumatic heart disease, that in a random group with

\* From the Cardiology Section of the Medical Service, Station Hospital, AAFTTC, Chicago

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† Instructor in Medicine, School of Medicine, University of Pennsylvania, Chief in Cardiology, Doctor's Hospital, Philadelphia, Chief of the Cardiology Section, Station Hospital, U S Army, Chicago

‡ Chief of Medical Service, Station Hospital, U S Army, Chicago

acute polyarthritis the information obtained from serial curves should offer an excellent objective means for differentiating rheumatic fever from other simulative diseases. The purpose of the present study is an attempt to test the validity of this view and to correlate other pertinent data bearing on the problem of acute rheumatic fever, as it is encountered in the military services

#### MATERIAL AND METHOD

During the period from January 1 to July 31, 1943, 135 soldiers, in whom acute migratory polyarticular rheumatism was the outstanding syndrome, were admitted to the Station Hospital, AAFTHC, Chicago. In most instances the arthritis was the primary cause for the hospitalization, but in occasional cases the original complaint was an acute upper respiratory infection, the arthritic manifestations becoming evident after the entry of the patients to the hospital. In the present study, beginning with the first such case, 100 consecutive admissions for acute polyarthritis were carefully analyzed. In this random group, all were young male adults who had been carrying on their usual military duties prior to the onset of their illness. Their ages ranged from eighteen to forty years, 81.4 per cent being thirty years or less in age. Because the findings obtained in this survey have served to establish the diagnostic criteria and epidemiological correlations subsequently applied to the entire series, the details of the method will be briefly described.

On the day of admission a complete history was obtained, especial emphasis being placed on the date of onset of the arthritic symptoms, the number of joints involved, the frequency of antecedent attacks of rheumatic infection, the presence or absence of cardiac pain, the location of the soldier at the time of onset of the arthritis, the home location, the familial incidence of rheumatic infection or rheumatic heart disease, and knowledge of any previous tonsillectomy. The same day a complete physical examination was performed by the authors, especial search being made for infected tonsils, joint disease, subcutaneous nodules, purpura or erythematous lesions, cardiac enlargement, adventitious sounds such as friction rub or murmurs, changing quality of the heart sounds, any irregularity of rhythm, a triplication of sounds in each cardiac cycle, and signs of cardiac failure.

Each subject was examined in the supine, sitting and lateral positions, before and after exercise, and with the breath held in various phases of respiration. This practice was found useful in identifying some of the conduction disturbances and in classifying a murmur. All diastolic murmurs were considered significant. However, because of the frequent finding of functional low-pitched systolic murmurs in healthy young adults, a systolic murmur was considered to be of organic origin only if it did not vary greatly with respiration, if it persisted in various body positions, if its maximum intensity was at the apex, if it was long and took up most of systole, if it was high pitched and had a swishing quality, and if it persisted throughout the period of observation.

Routine laboratory studies within the first twenty-four hours after the initial examination consisted of a urinalysis, complete blood count, erythrocyte sedimentation time, teleoroentgenogram and an electrocardiogram. Except in special circumstances, another electrocardiogram was not obtained until the following day. Afterwards, unless more frequent use of those laboratory procedures seemed to be warranted, further electrocardiograms and erythrocyte sedimentation determinations were obtained at weekly intervals.

An examination similar to the original one was conducted at frequent intervals by the authors during each patient's hospital stay.

All electrocardiograms were obtained with the patient in the recumbent position. Unless otherwise indicated, Lead CF-4 was the chest lead usually employed. Any changes noted could not be attributed to a drug because acetylsalicylic acid was the only medication administered to these patients.

The effect of a single large dose of atropine sulfate was also noted in several instances, serial tracings being obtained at ten-minute intervals within an hour after the subcutaneous administration of 2.5 mg. of this drug.

A portion of this study is an attempt to correlate the incidence of hemolytic streptococcal infections with that of rheumatic fever and scarlet fever. The criteria for the diagnosis of the latter disease consisted of the finding of a punctate, erythematous rash, a diffusely injected throat, pastia lines, circumoral pallor, coated tongue with denuded edges or a "strawberry" tongue later developing a "raspberry" appearance, all of which

would be followed by desquamation of the skin. In doubtful cases a Schultz-Charlton test was done.

#### THE DIAGNOSIS OF ACTIVE RHEUMATIC CARDITIS

In this series of 100 consecutive admissions exhibiting the syndrome of acute migratory polyarticular rheumatism, involvement of the heart was detected in 69 per cent. The means by which this was accomplished are discussed in detail below.

##### A. Physical Signs

These can broadly be placed in three categories, namely, those indicative of endocardial, myocardial and pericardial involvement. The detection of endocarditis was dependent on the elicitation of murmurs which could definitely be distinguished from the functional types that are so frequently heard among healthy young adults in the armed forces. The criteria for this distinction (v.s.) were rigidly adhered to, because it was believed that by this means errors would be minimized. The clinical detection of myocarditis could not be accomplished, in contrast with the situation in children, by the recognition of cardiac enlargement. More reliable for this purpose, it was discovered, was the identification of various disturbances of rhythm. The diagnosis of pericarditis was made in only one instance by the auscultation of the classical friction rub, even though 10 per cent of this series complained of precordial pain at one time or another during the illness. Despite the fact that the significance of a midsystolic click is of questionable diagnostic value,<sup>11</sup> a brief discussion of this adventitious cardiac sound is included because of its detection in two of the cases, manifesting other evidences of acute rheumatic heart disease. In the entire series active involvement of the heart could be *indisputably* recognized by clinical examination alone in a fairly large proportion, if signs of conduction disturbances rather than those of endocardial lesions are sought for (Table 3). This fact will become apparent in the more detailed analysis which follows.

1 *Significant Murmurs*—Adhering to the rigid criteria already described, significant murmurs were audible in only 17 per cent of this series. These were divided as follows: mitral systolic alone, 11 per cent, mitral systolic associated with an aortic diastolic, 4 per cent, and aortic diastolic alone, 2 per cent. It will be noted that no mitral diastolic murmurs were discov-

ered The correlation between the incidence of endocarditis and previous episodes of rheumatic infection can be stated thus Of the 17 per cent showing signs of endocārditis, only nine cases, roughly 50 per cent, gave a history of antecedent attacks of rheumatic fever Of the total number with clinical signs of endocarditis, 70 per cent (representing 12 per cent of this entire series) also showed substantiating electrocardiographic evidence of active carditis Stated differently, in the group in whom the presence of active carditis could be identified, this identification was based, in 72 per cent of the cases, on the recognition of an endocardial lesion alone On the other hand, in only 5 per cent of this entire series of 100 cases of acute polyarthritis the diagnosis of acute rheumatic heart disease was dependent purely on the finding of significant murmurs It should also be stated that in this group with endocarditis there was never any roentgen evidence of enlargement of any of the cardiac chambers

2. *Summation Gallop Rhythm*<sup>11</sup>—In 35 per cent of this series, usually at an early stage of the illness, a transient prolongation of the P-R interval with normal sinus rhythm was recorded in the electrocardiogram In about one quarter of this number, a summation type of gallop rhythm was audible In some instances this could be elicited by accelerating the cardiac rate by mildly exercising the patient in bed There was no correlation noted between the severity of the first degree heart block and the findings of summation gallop rhythm The latter was never elicited in the absence of a first degree heart block

3 *Varying Intensity of the First Heart Sound*—This sign was found useful in detecting the presence of auriculoventricular dissociation and hence active carditis, because it was found in one half of six cases in which this evanescent disturbance of rhythm was recorded in the electrocardiograph It never was present in the absence of this particular conduction disturbance

4 *Dropped Beats*—In all of the six instances in which the diagnosis of partial heart block with a Wenckebach phenomenon and dropped beats was made by means of the electrocardiograph, it was possible to predict the diagnosis by the finding of dropped beats on auscultation of the heart This type of conduction disturbance usually was present only in the early stages of the disease Its confusion with premature contractions was always easily eliminated if one excluded prematurity of the sound preceding the pause and also if one carefully listened for

summation gallop rhythm in occasional cardiac cycles, following the pause

5 *Premature Contractions*—These occurred in 5 per cent of the series and, as would be expected, there was a uniform correlation between the electrocardiographic and the clinical findings. They were always isolated and never appeared as runs of paroxysmal tachycardia. They never persisted after the acute infection had subsided. None of them were interpolated so that their clinical detection was easy.

6 *Sinus Bradycardia*—This occurred in 24 per cent of the series and, as would be expected, there was a uniform correlation between the electrocardiographic and the clinical findings. In each instance the heart rate was accelerated by mild exercise, but never to the extent which would occur normally. With the patient holding his breath there was no variation in intensity of the first heart sound, such as one elicits in complete heart block with similar slowing of the heart rate.

7 *Pericardial Friction Rub*—This was heard in only one instance, and in this case there was also a significant systolic mitral murmur without associated cardiac enlargement or detectable pericardial effusion in the teleoroentgenogram. Although transient inversion of T waves in Leads II and III occurred in the electrocardiogram of this patient, in seven other cases significant T wave inversions occurred without an accompanying friction rub.

8 *Cardiac Enlargement*—This was never discovered by the usual methods of physical examination in any of these individuals, including the patient in whom the teleoroentgenogram was able to demonstrate a slight and transient increase in the cardiac diameters. No reliance can therefore be placed on the clinical detection of transient cardiac dilatation during the course of acute rheumatic fever in the young adult.

9 *Midsystolic Click*<sup>11</sup>—This peculiar adventitious cardiac sound which was encountered in two of our cases had all the characteristics of an extracardiac phenomenon. It was localized to the cardiac apex in each instance. A striking characteristic was its marked accentuation with the subject sitting forward, disappearing with the subject in the recumbent position. This sound could easily be distinguished from the snappy first sound of mitral stenosis by the fact that it occurred in midsystole instead of early in systole, it became less intense rather than louder

when the patient assumed the left lateral decubitus position, and it was not associated with a mitral diastolic murmur. This sign is considered to be of questionable significance because it has been observed by the authors in normal young adults as well. On the other hand, in the two individuals in whom it appeared, other good evidence of cardiac involvement had been discovered.

## B Electrocardiographic Alterations

The transient electrocardiographic abnormalities considered to be diagnostic of active carditis were arbitrarily divided into two groups, the *unequivocal* and the *equivocal* (Tables 1 and 2). The former consisted of first degree heart block, with the P-R interval measuring 0.22 seconds or more, partial auriculoventricular heart block with a Wenckebach phenomenon and dropped beats, auriculoventricular dissociation, inversion of the T waves in leads other than Lead III, bundle branch block, S-T interval deviations, and transient notching of the P waves in Lead I. The equivocal alterations consisted of temporary sinus bradycardia, the rate ranging from 41 to 58, other types of T wave changes, such as blunting and notching of the apex or tall upright T waves in Lead CF-4, the height exceeding 10 mm, transient diminution of the QRS complexes without change in the electrical axis, premature contractions of nodal, ventricular or auricular origin, wandering pacemaker, and transient shift of the electrical axis to the left.

The reasons for this differentiation are that the changes in the latter group, although considered significant by many authorities, are not so considered by others. The alterations in both groups were of a transient nature and all of them usually, but not always, disappeared after the clinical manifestations of the acute stage of this infection had subsided. The influence of heightened vagal tone upon the conduction disturbances was demonstrated by the fact that, in all cases in which the experiment was tried, they were abolished following the administration of atropine sulfate (Table 4). No correlation was found to exist between the severity of the polyarthritis and the electrocardiographic alterations. Similarly, no correlation was found to exist between subjective symptoms such as cardiac pain or dyspnea and the electrocardiographic findings. The latter were not infrequently quite striking in those who had the fewest complaints. In spite of the fact that 64 per cent of this series

showed graphic evidences of acute myocarditis, a transient enlargement of the heart was noted in only one instance. Too, of this large number with positive electrocardiographic changes, residual valvulitis occurred in only 18.8 per cent.

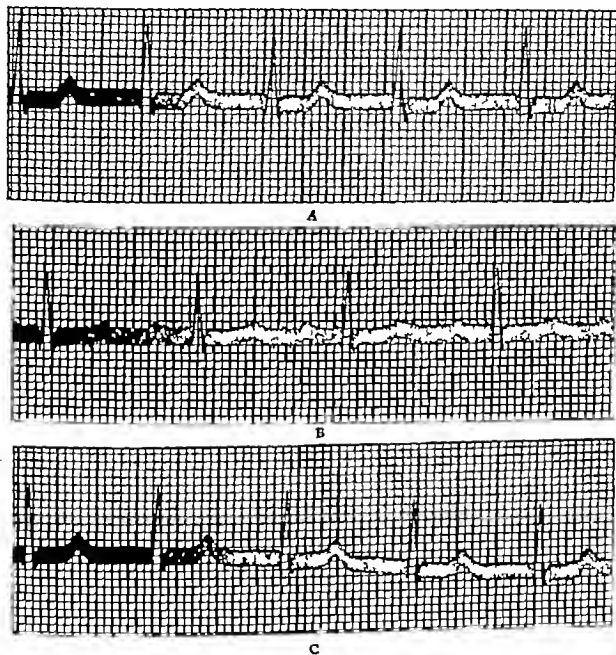


Fig. 28 (Lead II) —Transient nature of prolongation of the P-R interval associated with normal rhythm in early rheumatic fever. *A*, Present on admission of patient. *B*, absent in afternoon of same day. *C*, present again the following day.

1 UNEQUIVOCAL CHANGES —(a) *Prolongation of the P-R Interval Associated with Normal Sinus Rhythm* —Of all the various electrocardiographic changes, this was the most frequent, occurring in 35 per cent of this series. It appeared early in the course of the disease and usually disappeared as other manifestations of the infection subsided. On occasion however its ap-



TABLE 1

INCIDENCE (IN PER CENT) OF UNEQUIVOCAL ELECTROCARDIOGRAPHIC CHANGES DIAGNOSTIC OF ACTIVE CARDITIS IN 100 SOLDIERS WITH MIGRATORY POLYARTERITIS

Transient Changes	Antecedent or Subsequent Associated EKG Abnormalities															
	Total Incidence	Isolated Finding	T Wave Inversion	Notched P Wave	Intraventricular Block	Partial A-V Block with Dropped Beat	A-V Dissociation	Sinus Bradycardia	Tall Upright T <sub>1</sub>	Blunted or Notched T	Diminished Amplitude QRS	Premature Contractions	Changing Pacemaker	Shift in Axis to Left	Long P-R Interval	S-T Segment Deviations
Prolonged P-R interval with sinus rhythm (0.22-0.44 sec)	35	7	3	1	—	5	6	11	12	1	7	2	—	7	—	1
Partial A-V block with Wenckebach phenomenon and dropped beats	6	—	—	1	—	—	1	1	1	—	—	1	—	—	5	1
Auriculoventricular dissociation	6	—	1	1	—	1	—	2	3	—	1	1	1	1	6	—
Delayed intraventricular conduction	1	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—
Delayed intra-auricular conduction (notched P)	1	—	—	—	—	1	1	—	1	—	—	1	—	—	1	—
T wave inversions in Leads other than Lead III	8	4	—	—	—	—	1	1	1	1	—	—	—	2	3	1
S-T segment deviations	2	—	1	—	—	1	—	—	1	—	—	—	—	1	1	—



TABLE 3

SUMMATION OF PHYSICAL SIGNS AND ELECTROCARDIOGRAPHIC CHANGES SUGGESTIVE OF CARDITIS IN 100 SOLDIERS WITH MIGRATORY POLYARTHRITIS

	With Endocarditis	Without Endocarditis	With Corresponding Physical Sign	Without Corres- ponding Physical Sign
<i>Physical Signs</i>	Per Cent	Per Cent	Per Cent	Per Cent
Significant murmurs alone	5	—	—	—
Summation gallop	3	6	9	—
Varying intensity of first heart sound	1	2	3	—
Dropped beats	1	5	6	—
Friction rub	1	—	1	—
Sinus bradycardia	2	22	24	—
Premature contractions	1	4	5	—
Midsystolic click	1	1	2	—
<i>Electrocardiographic Changes</i>				
First degree heart block	7	28	9	26
Partial A-V heart block with dropped beats	1	5	6	—
Auriculoventricular dissociation	2	4	3	3
Delayed intra-ventricular conduction	—	1	—	1
Delayed intra-auncular conduction	1	—	—	1
T wave inversions	1	7	—	8
S-T segment deviations	1	1	—	2
Sinus bradycardia	1	1	—	—
Tall upright T <sub>4</sub>	2	22	24	—
Blunted and notched T <sub>4</sub>	8	10	—	18
Diminution in amplitude of QRS	—	2	—	2
Premature contractions	2	12	—	14
Wandering pacemaker	1	4	5	—
Shift in electrical axis to left	1	1	—	2
	3	8	—	11

TABLE 4  
EFFECTS OF ATRAPINE UPON HEART RHYTHM IN SIX CASES OF RHEUMATIC FEVER

Case No	Rhythm Before Exhibition of Drug	10 Min.	20 Min.	30 Min	40 Min.	50 Min	60 Min
1	Normal sinus mechanism with P R interval of 0.40 sec. Ventricular rate = 100	P R = 0.40 V.R. = 77.5	P R = 0.36 V.R. = 100	P R = 0.30 V.R. = 100	P R = 0.36 V.R. = 100	P R = 0.36 V.R. = 100	P R = 0.40 V.R. = 86
2	Normal sinus mechanism with P R interval of 0.40 sec. Ventricular rate = 67	P R = 0.40 V.R. = 67	P R = 0.36 V.R. = 67	P R = 0.28 V.R. = 83	P R = 0.28 V.R. = 83	P R = 0.34 V.R. = 88	P R = 0.36 V.R. = 83
3	Partial heart block with Wenckebach phenomenon—dropped beats			P R = 0.28 NSM V.R. = 94	P R = 0.26 NSM V.R. = 73	P R = 0.20 NSM V.R. = 79	
4	Partial heart block with Wenckebach phenomenon—dropped beats	Sinus rhythm Rate = 52 P R = 0.18	Sinus rhythm Rate = 136 P R = 0.18	Sinus rhythm Rate = 157 P R = 0.16		A V dissociation A.R. = 150 V.R. = 136	Sinus rhythm Rate = 136 P R = 0.18
5	Normal sinus mechanism with P R interval of 0.26 sec. Notched P wave in Lead I. Ventricular rate = 88	Notched P P R = 0.20 V.R. = 115	Notched P P R = 0.02 V.R. = 125	P normal P R = 0.20 V.R. = 125	P normal P R = 0.20 V.R. = 125	P normal P R = 0.20 V.R. = 120	
6	Normal sinus mechanism with P R interval of 0.32 sec. Ventricular rate = 115	P R = 0.26 V.R. = 115	P R = 0.18 V.R. = 115	P R = 0.18 V.R. = 125	P R = 0.18 V.R. = 125	P R = 0.18 V.R. = 125	

Key P R = P R interval in seconds, V R. = ventricular rate A.R. = auricular rate NSM = normal sinus mechanism

pearance or persistence was the only detectable evidence that the acute rheumatic state had not disappeared. Its inconstant and transient nature was clearly demonstrated in one case in which this change was recorded in the electrocardiogram obtained on the morning of the day of admission (Fig 28, A), being absent in the afternoon of that same day (Fig 28, B) and then reappearing on the following day (Fig 28, C).

First degree heart block was an isolated finding in only 7 per cent of this series, leaving 28 per cent which were associated with other electrocardiographic alterations (Table 1). In four cases with this type of change, serial tracings were obtained following the subcutaneous injection of 2.5 mg of atropine sulfate, and in each instance there was a significant though temporary reduction in the auriculoventricular conduction time (Table 4). The first degree heart block in this series varied from 0.22 to 0.44 second. However, the extent of the myocardial involvement could not be predicated from the length of the P-R interval because frequently other serious changes in the electrocardiograms were encountered in association with P-R intervals of normal or only slightly increased duration.

(b) *Partial Auriculoventricular Heart Block with Wenckebach Phenomenon and Dropped Beats*—This finding, which was never an isolated occurrence, appeared in 6 per cent of this series. The associated changes are seen in Table 1. This conduction disturbance appeared early in the disease and was always a transient phenomenon, being only one component of the acute rheumatic state, never persisting after other evidences of the acute infection had disappeared. In the single case in this entire series in which the teleoroentgenogram demonstrated evidence of temporary cardiac enlargement, this type of disturbance in rhythm was encountered. This suggests that it is probably indicative of fairly severe myocardial involvement. The maximum length of the P-R interval associated with the Wenckebach phenomenon in these cases usually did not equal and never exceeded the auriculoventricular conduction time in many instances associated with first degree heart block and normal sinus rhythm. It was also observed in three individuals in whom a transient partial heart block with dropped beats was recorded, that during the stage of the partial heart block with Wenckebach phenomenon the maximum P-R interval was less than that which appeared when a normal sinus rhythm was subsequently re-

stored In the two cases in which the experiment was tried, this conduction disturbance was temporarily abolished by the subcutaneous administration of 2.5 mg. of atropine sulfate (Table 4)

(c) *Atriculoventricular Dissociation*—This disturbance in rhythm occurred in 6 per cent of this series. It was never an isolated finding, and usually appeared early in the disease. The other types of electrocardiographic abnormalities which either preceded or followed its appearance are seen in Table 1, but of these a prolonged P-R interval was a constant association. The ventricular rate encountered in this series with this conduction disturbance ranged from 65 to 100

(d) *Delayed Intraventricular Conduction*—It occurred only once and was manifested by a widened S pattern. The only associated change consisted of ventricular premature contractions

(e) *Delayed Intra-auricular Conduction*—This was manifested by a notched P wave in Lead I. It occurred only once. Interestingly enough, it was not present in the early tracings of this individual, but appeared only in subsequent serial electrocardiograms. It was temporarily abolished following the subcutaneous administration of 2.5 mg. of atropine sulfate (Table 4). Associated electrocardiographic changes are recorded in Table 1

(f) *T Wave Inversions*—These can be divided into two groups, namely, those occurring in the precordial lead alone (4 per cent) and those found only in the limb leads (4 per cent). Peculiarly enough, the two never coexisted. Among this 8 per cent the inverted T waves were an isolated finding in one half of this number. The changes associated with the other 4 per cent are listed in Table 1. In the limb leads, the inversion was noted in Leads I and II in one case, and in Leads II and III in the remainder. Eventually in all but one case the negative T waves disappeared, the time for this evolution varying from seven to thirty-nine days. In only one case of the entire group, the T wave inversion was preceded by an elevation of the S-T segment. In one case in which a negative T wave appeared as an isolated finding in Lead CF-4, the polarity of T became positive within several days and then subsequently without any other evidences of rheumatic activity, it again became negative, and shortly thereafter returned to its normal position. In one of the cases with inverted T waves in the limb leads a pericardial friction rub was audible, but x-ray examination failed to

show any enlargement of the cardiac shadow Too, there was no cardiac enlargement in the teleoroentgenogram in any of the other cases with T wave inversion Physical signs in the heart were lacking in the 4 per cent manifesting a negative T wave in the precordial lead In all cases in which this change occurred in Lead CF-4, the possibility of malposition of the exploring electrode in its production was always carefully excluded

(g) *S-T Segment Deviations*—These occurred in 2 per cent of the entire series In one instance they consisted of slight depressions in Leads II and III, being the only evidence of an acute myocardial involvement until a partial auriculoventricular heart block with a Wenckebach phenomenon appeared in subsequent tracings In this case no changes in polarity of the T wave were ever noted In the other instance the S-T changes consisted of elevations in Leads II and III, these were subsequently succeeded by inversion of T in these same leads In the latter case, no clinical evidence of pericarditis was ever noted An endocardial lesion was not manifest in either instance

2 EQUIVOCAL CHANGES—(a) *Sinus Bradycardia*—This occurred in 24 per cent of this series, being an isolated finding in only 5 per cent In this group the rate ranged from 41 to 58 per minute, eventually returning to normal in each instance The associated changes are listed in Table 2 Attention is invited to the large number of associated changes dependent on increased vagal tone, such as first degree heart block, partial heart block and auriculoventricular dissociation

(b) *Tall Upright T waves in the Precordial Lead (CF-4)*—Upright T waves exceeding 10 mm in the precordial lead were encountered in 18 per cent of this series They were an isolated finding in only 3 per cent, and almost always were an accompaniment of significant electrocardiographic alterations These are listed in Table 2

(c) *Blunted and Notched T wave in the Precordial Lead (CF-4)*—This finding appeared in 2 per cent of the series In neither instance was it an isolated finding Vagal effects such as sinus bradycardia and first degree heart block were accompanying disturbances in one instance, and in the other an inversion of T subsequently appeared (Table 2) The incorporation of a P wave in the T wave as a cause for this appearance of the T wave was considered but easily excluded in both instances

(d) *Diminution in Amplitude of QRS in the Limb Leads In-*

*dependent of Changes in the Electrical Axis*—This finding appeared in 14 per cent of this series, never occurring as an isolated phenomenon (Table 2) The significance of this change can be judged from the fact that of the entire group, 7 per cent manifested it in conjunction with a first degree heart block. It was never associated with evidences of pericarditis with or without effusion.

(e) *Premature Contractions*—These occurred in 5 per cent of the series, being an isolated finding only once (Table 2) The ectopic foci occurred in the auricle, the ventricle and the auriculoventricular node. In this series they never gave rise to a paroxysmal tachycardia. They never persisted after the beginning of the convalescent stage of the acute rheumatic state.

(f) *Wandering Pacemaker*—This occurred in 2 per cent of the series. Its significance, however, can be judged from the fact that in one case it was associated with an aortic diastolic murmur and in the other with a first degree heart block which later eventuated in an auriculoventricular dissociation.

(g) *Shift in the Electrical Axis to the Left*—This occurred in 11 per cent of this series, being an isolated finding in only 3 per cent (Table 2). Accompanying changes consisted or prolonged P-R intervals (7 per cent), auriculoventricular dissociation (1 per cent), inverted T waves in leads other than Lead III (2 per cent), sinus bradycardia (6 per cent), diminished amplitude of QRS (3 per cent) and sinus bradycardia (6 per cent). It was also striking that a shift in the electrical axis to the right was only rarely encountered.

### C Symptoms Suggesting Cardiac Dysfunction

The only such symptom encountered in this series was pain in the region of the heart. It occurred in 10 per cent of the cases, but was never sharp, being described as a dull oppression over the precordium. Of the ten cases with this symptom, seven had unequivocal electrocardiographic evidence of active carditis, and two others had clinical signs of heart disease. It was associated with a pericardial friction rub only once. On the other hand, 59 per cent in this series had good evidence of cardiac involvement without ever complaining of precordial distress. The absence of this symptom therefore warrants no conclusions, but its presence should suggest, in cases of polyarticular rheumatism the existence of a complicating myocarditis.



## D X-Ray Findings

In this series, the teleoroentgenogram showed evidence of cardiac enlargement in only one case. This was of a transient nature and disappeared within seven days. It was not due to pericardial effusion. This patient also complained of precordial pain and in his electrocardiogram a transient partial heart block was discovered. The teleoroentgenogram, in young adults with acute polyarthritis, therefore can not be considered an important adjunct in establishing the diagnosis of rheumatic fever.

## EPIDEMIOLOGIC CONSIDERATIONS

1 *Age*—As has been stated, 69 per cent of this series of 100 consecutive admissions with acute polyarthritis showed positive evidence of acute carditis. In this positive group, the ages ranged from eighteen to forty years. Those below the age of thirty predominated, representing 81.2 per cent of the total number. Of those with endocarditis, only four were above, whereas the other thirteen were below the age of thirty. Regarding the incidence of a history of antecedent rheumatic infection, the figures in those above and below the age of thirty are comparable, being 30.8 per cent in the former, and 32.1 per cent in the latter group.

2. *Race*—No cases were discovered in Negroes even though during the period under consideration the hospital population among which this study was conducted constantly received Negro soldiers from a camp near Chicago, whenever any illness requiring hospitalization developed among them.

3 *Familial Incidence*—In this group with acute rheumatic fever, a history of rheumatic fever or of rheumatic heart disease in members of the immediate family was obtained in 32 per cent. In contrast with this incidence, in those with acute polyarthritis without evidence of active carditis a familial history of rheumatic infection occurred in only 1 per cent.

4 *Home Location*—Those cases among this series manifesting evidence of acute rheumatic fever (cf ) had lived in various sections of this country prior to their entry into the Army, although the predominant number came from the midwestern states. This is especially interesting inasmuch as all in this group, with almost no exceptions, developed the acute polyarthritis in or within a relatively short distance of Chicago. The frequency distribution among those with active carditis was found to be as

follows 49.3 per cent came from the midwestern states, 23.2 per cent came from the eastern states, 17.4 per cent came from the southern states, and 10.1 per cent came from the far western states.

*5 Antecedent Rheumatic Infection*—There are striking contrasts between the group with polyarthritis and carditis and those with polyarthritis alone as regards a history of antecedent attacks of rheumatism. In the former group, a positive history was obtained in 40 per cent and in the latter, in 29 per cent. Although this difference hardly seems significant, the importance of antecedent rheumatic infection in the development of an active carditis with a subsequent attack of polyarthritis is emphasized by the fact that of the entire series with acute polyarthritis, 75 per cent of those giving such a history showed evidence of involvement of the heart during the current episode of acute rheumatism. Of those manifesting signs of endocarditis, only 41.1 per cent gave a history of antecedent rheumatic infection.

*6 Relation to Antecedent Upper Respiratory Tract Infections*—In the present series, considering the cases individually, a history of acute sore throat one to two weeks preceding the appearance of the joint manifestations was obtained in every instance in which the diagnosis of acute rheumatic fever was subsequently confirmed by methods which are described above. However, because the sore throat was usually not severe, the majority of them (87 per cent) did not come to the hospital until the joint symptoms appeared. The exceptions were the 13 per cent who had been admitted because of an acute pharyngitis or acute tonsillitis, the joint pains developing during their convalescence from the respiratory infection.

Analyzing the cases collectively it will be noted (Fig. 29) that the peak incidence of rheumatic fever, plotting the cases according to the onset of the joint symptoms, closely paralleled the peak incidence of acute tonsillitis and pharyngitis in the same hospital population.

*7 Relation to Hemolytic Streptococcal Infection*—An approximation of the prevalence of hemolytic streptococci in cases of acute tonsillitis and pharyngitis was obtained for the Chicago area, from figures supplied by the University of Chicago, where throat cultures were routinely employed in all cases among the student body who complained of acute sore throat.

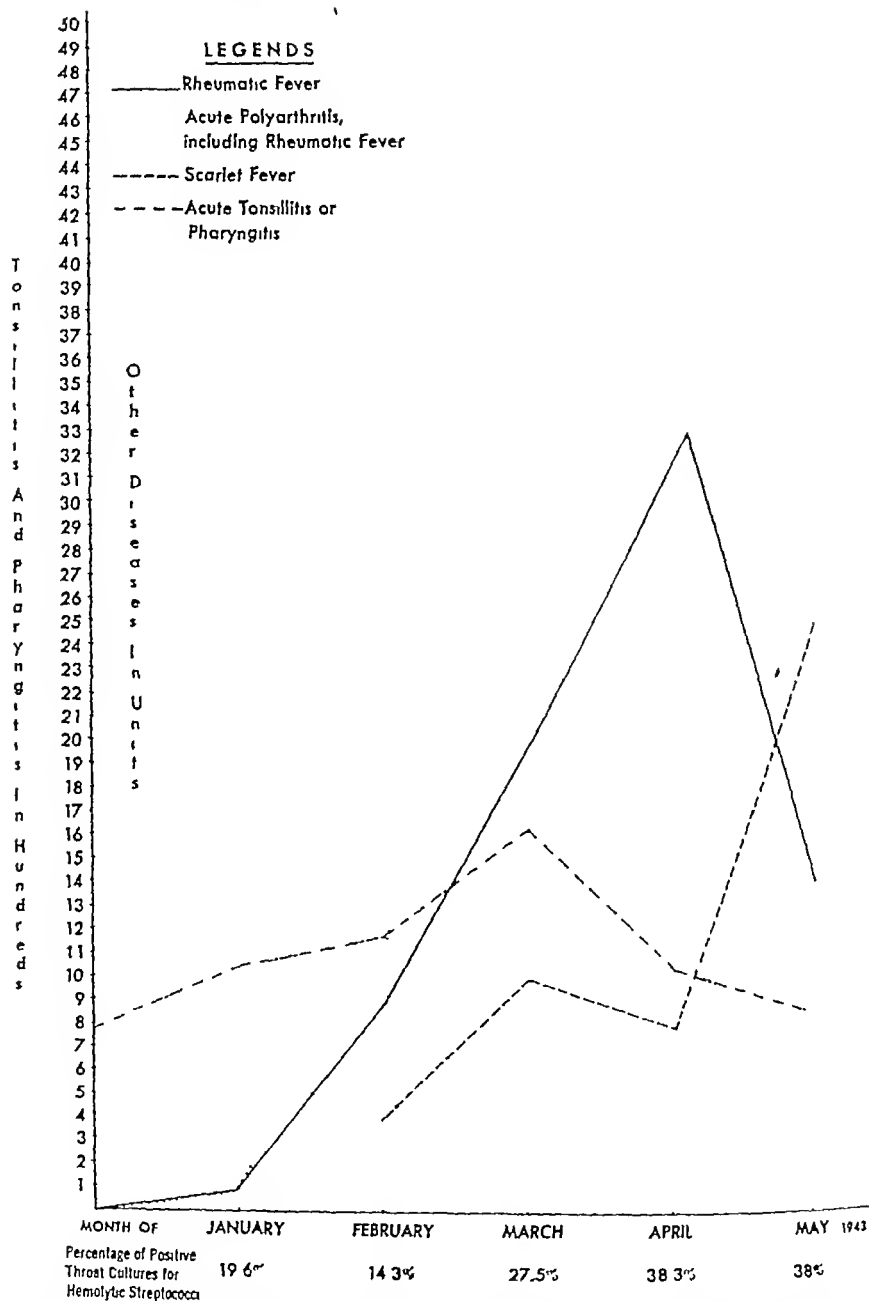


Fig 29—Increased frequency of acute rheumatic fever accompanying a rising incidence of hemolytic streptococcal infections For explanation see text.

These figures and their distribution for the first five months of 1943 are shown as percentages in Figure 29 By simple conversion, with the aid of these figures, the monthly incidence of



37.3 per cent had had one or more antecedent attacks of rheumatism, while 62.7 per cent had not. During the current episode of polyarthritis, positive evidence of acute carditis was obtained in 70.6 per cent of those with retained tonsils and in 63 per cent of those whose tonsils had previously been removed. Conversely, of the total number of cases of acute rheumatic fever in this series, 55.4 per cent had retained tonsils, while 44.6 per cent did not. This difference is hardly significant.

9 *Trauma*—In several instances, the patients stated that the first joint to become swollen and painful was one which had been injured a day or two preceding the onset of the arthritis. The significance of this cannot be stated at this time.

10 *Diet*—Inasmuch as all of the patients in this series had been eating the usual nutritious and well-balanced diet provided by the Army mess, lack of any dietary factor would not appear to be of any influence in predisposing these individuals to the acute polyarthritis.

#### TREATMENT AND PROGNOSIS

Immediately after their admission the patients were started on a regimen of 20 grains of acetylsalicylic acid every four hours. No case appeared to be resistant to acetylsalicylic acid and in no instance was it necessary to resort to amidopyrine or narcotics for relief of pain. No sodium bicarbonate was given with the acetylsalicylic acid and in no instance was there evidence of gastric irritation or rashes due to the drug. Several times daily methyl salicylate was gently rubbed into the involved joints after which they were covered with flannel. A cradle was used when the lower extremities were involved but no external heat was applied. No splints were used and no physiotherapy was necessary. Joint swelling and pain disappeared in a large degree in all cases, within a few hours or, at the most, forty-eight hours after admission.

The diet was the ordinary hospital diet consisting of approximately 3000 calories a day with a normal intake of fluids. This diet was not reinforced with any of the vitamins due to its excellent variety.

There was general nursing care of all cases. Bed rest was compulsory until the patients appeared clinically well and the sedimentation rates and electrocardiograms were normal for three successive weeks. Weekly sedimentation rates and weekly

electrocardiograms were done throughout the period of hospitalization. Neither of these diagnostic procedures was relied upon separately because a significant proportion of the cases showed progressive changes in the electrocardiograms even though the sedimentation rates were normal, and vice versa. For this reason it was deemed advisable to insist on both normal sedimentation rates and normal electrocardiograms for three successive weeks before the patients were allowed out of bed. Once they were allowed out of bed, graduated exercises were given, and in most instances three more weeks of hospitalization were required. Upon discharge from the hospital a convalescent furlough of four weeks was given, provided there was no evidence of endocarditis. Following this furlough the patient was placed on limited service. If there was evidence of endocarditis present in the form of diastolic or significant systolic murmurs, the patient was recommended for an honorable discharge from the Army. The average hospital stay was seventy days.

The hospital is staffed with volunteer workers for supervision of occupational therapy. During convalescence these patients had periods of occupational therapy which stressed the fact that physical activity could be indulged in with no untoward effects. The result was that in no case was psychotherapy necessary because of any form of cardiac neurosis.

In spite of significant electrocardiographic changes in many cases (64 per cent) the clinical recovery and disappearance of these changes was striking in all instances. Of the 64 per cent in whom various transient abnormalities occurred in the electrocardiogram, only 18.7 per cent of this number developed signs of a residual endocardial lesion. No cases developed a pericardial effusion.

Although a thirty-day follow-up examination of all patients discharged from the hospital has failed to show evidence of progressive cardiac damage, re-examinations at a later time are planned in order to establish definitely the fact that healing of the acute myocardial lesions of rheumatic fever can occur without subsequent valvular damage or enlargement of any of the chambers of the heart.

Although the treatment stresses simplicity, the results seem to warrant noting five important factors: (1) Acetylsalicylic acid in sufficient doses will keep the patient comfortable. (2) Bed rest and good nursing care are necessary if there is any evidence of

active infection as shown by clinical examination, sedimentation rate, and the electrocardiogram (3) A well-rounded diet of 3000 calories keeps up the nutrition and makes it unnecessary to add extra vitamins (4) Occupational therapy during convalescence is invaluable to dispel any chance of cardiac neurosis and frustration (5) Protection of the individual patient by a follow-up study and placing him upon limited service should minimize the chances of recurring rheumatic fever This plan allows for a better disposition of those cases remaining in the service

### CONCLUSIONS

1 The validity and reliability of the electrocardiograph in establishing the diagnosis of acute carditis among a random group of patients with acute migratory polyarthritis is demonstrated, provided serial and frequent curves are obtained in each instance.

2 In this study a large variety of nonspecific electrocardiographic abnormalities in the limb leads were noted Their relative incidence and importance are discussed The significance of isolated T wave changes in the precordial lead, indicative of active carditis, is also emphasized

3. Significant electrocardiographic changes were observed in 64 per cent.

4 Because of the high incidence of functional systolic murmurs in young adults, a clear definition of a significant murmur was made Adhering to such criteria, evidence of valvulitis was found in 17 per cent

5 Cardiac enlargement was observed in only one instance

6 The clinical recognition of active carditis is shown to be more dependent on the detection of disturbances in rhythm rather than on murmurs or cardiac enlargement.

7 The difference in the manifestations of acute carditis in children and in the adult is emphasized This fact has an important bearing on the diagnosis of acute rheumatic fever in the armed forces

8 The high incidence of healing of the acute myocardial process in rheumatic fever is demonstrated.

9 A brief discussion of the midsystolic click as it relates to acute rheumatic heart disease is included

10 Confirming previous reports, the influence of heightened vagal tone, relatively or absolutely, in the production of some

of the electrocardiographic changes in acute rheumatic carditis is demonstrated

11 Some of the epidemiological aspects of rheumatic fever are discussed. The relationship of this disease to hemolytic streptococcal infections is emphasized

12 All correlations are based on a minimal incidence of rheumatic fever in a single hospital population because of rigid objective criteria required by the authors for the diagnosis

13 Some of the phases in treatment and prognosis are discussed

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# SYMPOSIUM ON DISEASES OF THE BLOOD AND BLOOD-FORMING ORGANS

## INTRODUCTION RECENT ADVANCES IN THE DIAGNOSIS AND TREATMENT OF BLOOD DISEASES

LEROY H SLOAN, M.D., F.A.C.P.\*

It is a great pleasure to write this introductory word to the symposium on diseases of the blood presented herewith by a group of hematologists and clinicians in active daily contact with a large number of patients affected by disease of the blood-forming tissues and blood elements

There has been a steady and rapid progress in recent years both in the recognition of and therapy for such diseases. Thus progress has been spiced by epochal rises and spectacular peaks such as (1) Minot and Murphy's discovery of the essential element in the therapy of pernicious anemia, (2) the established relation of vitamins C and K to hemorrhagic states, (3) the value of splenectomy in primary thrombopenic purpura and (4) the use of the roentgen ray and irradiated phosphorus in leukemia. Back of such progress there has been a long detailed study of the origin of the normal blood cell, the morphology of diseased cells, the morphology of the cells obtained on bone marrow aspiration and the clinical application of these studies to therapy.

In the Chicago region the study of diseases of the blood has always engaged the attention of able clinicians. B. W. Sippy, whose fame rests largely on his treatment for ulcer, began his work with a study of splenic anemia. J. B. Herrick, eminent cardiologist, was the first hereabouts to describe sickle celled anemia, and Frank Billings gave close observation to the therapy

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\* Professor of Medicine, University of Illinois College of Medicine, Attending Physician, Cook County Hospital, Head of the Department of Medicine, Illinois Central Hospital

of Hodgkin's disease and leukemia and wrote on the neurological features of pernicious anemia. Williamson of the University of Illinois was at all times deeply concerned with methods for the more accurate determination of the hemoglobin content of the blood as well as in the clinical recognition of blood diseases. Karl Koessler was able to produce in experimental animals an anemia with changes resembling those found in pernicious anemia. This anemia was prevented by adequate vitamin content in the diet. With this nutritional basis he began to treat patients with pernicious anemia with a diet rich in vitamins. Six of his first patients were from my service at the Illinois Central Hospital. These patients all recovered upon a diet high in vitamins, rich in calories and of general character. This diet contained liver. Both Koessler and Minot and Murphy published their results in the same issue of the *Journal of the American Medical Association*. The significance of Koessler's work was lost in the larger significance of the discovery of Minot and Murphy of the curative value of liver. Today we view Koessler's work with greater consideration since the significance of vitamin loss becomes daily more apparent and the important place of vitamins in the therapy of states associated with anemia is recognized.

The discovery of the necessary element in the therapy of pernicious anemia was of prime importance. The elaboration of the technic of preparation, the concentration of the material and the continued efforts of Minot, Murphy, Cohn, Castle, Sturgis and others were, of course, the spur to renewed effort in the therapy not alone of pernicious anemia but also of the other anemias. Relatively soon one found that anemias could be roughly classified therapeutically into those amenable to liver, those requiring only iron for improvement, and those not responsive to either. The concentration of liver extracts, the use of the gastric mucosa, the addition of vitamin B as brewers' yeast—these and many other improvements are an old story.

The criticism of the older hematologists was that they were pure morphologists—that they smeared and looked, reported what they saw, and smeared again. Little by little, hereabouts men turned to the *origin* of the blood cell. During the all-too-short residence of Maximow amongst us, added zeal was well repaid as they followed the clinical significance of his studies and made use of them.

It was probably Richard Jaffe, eminent pathologist and master

teacher, who more than any other brought to this center a clearer knowledge of the origin of normal cells, of the classification of the blood dyscrasias, and of the pathology and prognosis of such diseases. He "popularized the study of the blood dyscrasias" and developed in the younger men under him and in those who came to his brilliant clinics the over-all picture.

The older classification into acute and chronic disease still gives the busy practitioner an instrument for rapid use. In the *acute* disease he expects to find signs and symptoms of a toxemia—fever, apathy, loss in weight, chills, hemorrhages, sweats, progressive weakness, and so forth. This is true in acute leukemia (stem cell, and other varieties), agranulocytosis and thrombocytopenic purpura.

In the *chronic* type he expects to find a slow progress of a relatively benign state with symptoms not necessarily of an anemia. Surprising indeed is the physical strength of some patients with pernicious anemia with counts of only 1,000,000. The patient with florid polycythemia may be disturbed not by his disease but by the questions of his friends, and when he finally develops signs they are in the nervous system and are due to thrombosis in vessels carrying a viscid, packed, slowly moving body of cells.

In pernicious anemia the patient complains of symptoms due to disturbance in the posterior and lateral tracts of his spinal cord—symptoms such as numbness, tingling and paresthesia. And so in the advanced iron deficiencies, in fact in the old chlorotics, the usual constipation and weakness were but a triviality compared to the venous thromboses seen in the retina. The chronic leukemic complains of swollen glands or enlarging abdomen as often or more often than he complains of weakness and loss of weight.

To the busy practitioner the general appearance of the patient is of great help. He recognizes the "cyanotic lividity" which Osler stressed in the patient with *polycythemia* with the chronic conjunctivitis, the overfilled retinal vessels, the bluish red tongue, the soft palate studded with punctate redness, the gingivitis, the varicose veins and the enlarged spleen. The "lemon pallor" of the patient with *pernicious anemia* is perhaps a little less evident in these days because the diagnosis is usually made much earlier and therapy given in adequate amount at an equally early stage. The "limey green" of advanced *chlorosis* is also less obvi-

ous these days when patients are already supersaturated with vitamins of all sorts, but the "waxy smoothness" of the skin of the patient with *leukemia* is still in evidence with his enlarged glands, enlarged spleen, increased metabolic rate, history of loss of weight and retinal sunburst.

The bleeding gums and sore throat do not mean pyorrhea to the physician of today but point to *agranulocytosis* or to *thrombopenia* or perhaps to *scurvy*. The enlarged glands of the neck or the groin or the axilla instantly bring forth the possible diagnosis of one of three major conditions, leukemia, Hodgkin's disease or lymphosarcoma, with the less common tuberculous gland still a possibility.

The patient with a blood dyscrasia shows involvement of many tissues of the body. Usually at some stage one finds almost every system and cell involved in one form or another. For example, we have the retinal changes of leukemia, of thrombocytopenia, of hemorrhagic states, the diffuse adenopathy of chronic lymphatic leukemia, the more localized adenopathy of Hodgkin's disease, the enlargement of the spleen in myeloid leukemia and less often in lymphatic leukemia, but also in Hodgkin's disease and in polycythemia, the sclerosing osteitis of Hodgkin's disease, the amyloidosis of the same disease and of the leukemic states, the thromboses of the brain in polycythemia and in leukemia, and the subarachnoid hemorrhage seen in thrombocytopenic purpura—all evidence of the diffuse involvement of the tissues and systems in disease pictures which are seemingly far apart. The study of the patient with a blood dyscrasia today involves a study of the patient himself and numerous examinations of the blood, of the sternal marrow, of the sedimentation rate, the clotting time, the bleeding time, of many smears and still other tests. It is not a study of the blood stream alone but of the whole system, with biopsy of glands where indicated.

The group of clinicians whose views are herewith presented represent those in active charge at our teaching centers. Alt brings the flavor of eastern influence and a large clinic at Northwestern, Davidsohn, a long and distinguished career in hematology, in transfusion reactions, in paternity tests, blood typing and now the Rh factor; Isaacs, the views of his own group at Michael Reese shaded by the previous contact with the group at Michigan, Potter, the experience of an able clinician at Billings engaged in special problems in a new and partially explored

field, Limarzi the teachings of Jaffé, of Williamson and the large and active clinic at Illinois, and Schwartz a large experience at Cook County Hospital where *every* patient is accorded a blood count and the dyscrasias are given special attention

Every day there is an enlarging armamentarium brought to this important field To select the chaff from the oats becomes our problem as clinicians

## THROMBOCYTOPENIC PURPURA

LOUIS R. LIMARZI M.D.\*

A marked tendency to bleed from the mucous membranes and into the tissues and skin with the formation of petechiae and ecchymoses is a prominent feature of a number of conditions. In some of the hemorrhagic conditions the bleeding tendency is the symptom of a recognized disease, while in another group the bleeding manifestations appear to be the primary feature of the disease.

The mechanism of abnormal bleeding usually involves one or more of the following factors<sup>20</sup> (1) quantitative or qualitative changes of the platelets, (2) disturbances in the clotting mechanism, and (3) increased permeability of the capillary wall.

In general, three organs or tissues are primarily concerned in the hemorrhagic disorders. They are the *bone marrow megakaryocytes*, which produce the blood platelets and in turn furnish the thromboplastin, the *liver*, which supplies prothrombin, fibrinogen and heparin, and the *blood vessels* with their endothelial function and capillary reactions. The spleen is a disturbing factor in some thrombocytopenic states and the gastrointestinal tract participates in the mechanism of vitamin K formation and absorption.

A history of any familial or hereditary blood disease in the family, a review of recent contact with drugs, chemicals or physical agents such as x-rays or radium, a thorough search for any dietary deficiency or allergic manifestation to foods, and inquiry as to recent contacts with any active or convalescent disease are important facts to note in attempting to formulate a working diagnosis in purpuric states.<sup>20</sup>

For the differentiation of the various types of hemorrhagic diseases there are necessary not only a full history, physical

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\* Assistant Professor of Internal Medicine, University of Illinois College of Medicine, Associate Attending Physician, Department of Medicine, Research and Educational Hospitals, Consultant in Hematology. Research and Educational Hospitals and Hemotin Hospital.

examination and the usual study of the blood, especially of the cellular elements, but in addition (1) an accurate platelet count, (2) bleeding time, (3) coagulation time, (4) retractivity of the blood clot, (5) determination of the prothrombin time as evidence of a deficiency of vitamin K,<sup>40</sup> (6) determination of the ascorbic acid in the blood as an indication of vitamin C deficiency, (7) the capillary resistance test (Rumpel-Leede) and (8) examination of the sternal bone marrow

Abnormal bleeding is due to many factors. It is therefore imperative to determine the underlying cause of the bleeding process before therapy is instituted. This is especially true in essential (primary) thrombocytopenic purpura, a disease in which splenectomy results in a cure. Many failures from splenectomy in the past in cases diagnosed "purpura hemorrhagica" have occurred because of incorrect diagnosis.

#### CLASSIFICATION OF THE PURPURAS

Classification of the purpuras is very difficult, because various combinations of many factors may be involved in any one group of cases.<sup>32</sup> In all, the changes in the capillary endothelium are probably much more important than the changes in the blood.

#### CLASSIFICATION OF THROMBOCYTOPENIC PURPURA

(Modified from Wintrobe<sup>53</sup> and Rosenthal<sup>41</sup>)

- I "Primary" or "essential" purpura haemorrhagica (Verlhof's disease)
  - (a) Thrombocytopenic purpura—acute
  - (b) Thrombocytopenic purpura—chronic
- II Secondary or symptomatic thrombocytopenic purpura
  - 1 Blood diseases
    - (a) Anemias Acute or chronic "primary" or "idiopathic" aplastic anemia, acute or chronic secondary aplastic anemia due to chemicals or physical agents, myelophthisic (tumors such as carcinoma, sarcoma, myelomas, etc., osteosclerosis, etc.), pernicious anemia, erythroblastosis (due to the Rh factor), sickle cell anemia, hemolytic anemia of unknown origin
    - (b) Leukemias Acute stem cell, acute myeloid, lymphatic or monocytic leukemia, late or terminal stages of chronic leukemia
    - (c) Disorders associated with splenomegaly Banti's syndrome, Gaucher's disease, Felty's syndrome, hemolytic icterus (spherocytic jaundice), rarely Hodgkin's disease, thrombophlebitis of portal and splenic veins, "idiopathic" splenomegaly and cirrhosis of liver with secondary splenomegaly
  - 2 Infections (acute and chronic) Septicemia, subacute bacterial endocarditis, typhoid fever, meningococcal sepsis, pneumonia, abscess of the lung, diphtheria, gangrenous pharyngitis, scarlet fever, tuberculosis, syphilis, etc

- 3 Intoxications Quinine, benzol snake venom, pertussis vaccine, mercury bichloride, organic arsenicals, gold salts, sulfonamide drugs, sedormid colchicine,<sup>44</sup> phenobarbital dinitrophenol ergot, bismuth iodine, organic hair dyes and "leg stocking color"<sup>45</sup> preparations
  - 4 Radiation Roentgen ray radium
  - 5 Jaundice Hepatitis, cirrhosis of the liver without splenomegaly
  - 6 Chronic nephritis with marked nitrogenous retention, extrarenal azotemia
  - 7 Foods andorris root
- III Congenital thrombocytopenic purpura

#### LABORATORY PROCEDURES TECHNIC AND INTERPRETATION

The technic of the practical laboratory procedures and their interpretations with relation to thrombocytopenic purpura follow

##### Bleeding Time (Duke's Method)

A small stab wound is made in the finger or the lobe of the ear and at half-minute intervals the blood is clotted up with a piece of heavy filter paper until bleeding ceases. The cut should be such that the diameter of the first blot is approximately 2 cm. without squeezing. The filter paper should touch the drop of blood which forms and the filter paper should not come in contact with the skin. Normally there are about 6 drops on the filter paper, gradually decreasing in size. Each drop represents the flow of blood in half a minute. The usual normal bleeding time is one to three minutes. The bleeding time determined in this manner does not necessarily express the hemostatic power of every tissue in the body.<sup>31</sup> Repeated determinations should be made. In purpura haemorrhagica where the blood platelets are reduced the bleeding time is extended from ten to ninety minutes.

##### Coagulation Time

Coagulation consists mainly in the transformation of fibrinogen into fibrin by means of a ferment called thrombin. The resulting clot is made up of a meshwork of fibrin with the entangled formed elements of the blood. The clear fluid expressed from this clot is the blood serum. There are several methods for the determination of the coagulation time and these vary in their results. Some methods are more simple than others, but less accurate. Howell's method is simple and accurate. With this little stasis as possible 5 cc. of blood is drawn by venipuncture into a dry syringe, which has been washed out with an ether petro-



latum mixture, the ether being allowed to evaporate, and the syringe thus being coated with a thin layer of the oil. The blood is expelled carefully into a clean dry sterile Wassermann tube 21 mm in diameter, care being taken to prevent the formation of air bubbles. The tube is tilted every two to three minutes and when the tube can be inverted without the blood flowing out, coagulation is considered complete. Normal blood coagulates by this method in ten to thirty minutes. In thrombocytopenic purpura the coagulation time is normal, but the clot does not retract or does so only very slowly.

### Clot Retraction

Approximately 5 cc of blood is run into a clean dry sterile Wassermann tube and allowed to stand at room temperature without being disturbed. The tube is observed at the end of each hour for six hours and at intervals of six to twelve hours thereafter. Beginning retraction is noticed in normal blood in one to two hours and the clot normally retracts completely within eighteen to twenty-four hours. In a normal blood, after the lapse of eighteen to twenty-four hours, a firm retractile clot is formed which, by virtue of its firm foundation, squeezes out a clear serum that can readily be poured off from the clot. The small firm clot can withstand considerable agitation. In thrombocytopenic purpura there is a delay in retraction, or a failure of the clot to retract due to a decreased number of platelets. The clot is soft and squeezes out only a small amount of serum.

### Platelet Count

The blood platelet fluid of Rees and Ecker is used. A small amount of diluting fluid (sodium citrate, 3.8 gm, formalin, 37 per cent reagents, 0.2 cc, brilliant cresyl blue, 0.1 gm, distilled water, 100 cc) is drawn into the bulb of the standardized erythrocyte pipette to moisten the capillary. The blood is then drawn up to 0.5 mark and the pipette diluted to the 101 mark with platelet diluting fluid. After shaking for two minutes, a certified counting chamber with improved Neubauer ruling is filled and allowed to stand for ten minutes. The counting and calculation are done as for a red cell count. The normal platelet count is from 200,000 to 400,000 per cu mm.

The normal life of a blood platelet is about three to five days. The chief function of the blood platelets appears to be their

control over the process of coagulation. Blood platelets are apparently the chief source of prothrombin of the plasma, probable source of at least part of the thromboplastic substance of the tissues and they bring about retraction of the clot. In thrombocytopenic purpura the blood platelets may be totally absent.

#### Capillary Resistance Test (Rumpel-Leede)

A blood pressure cuff is placed on the upper arm and the pressure maintained just above diastolic pressure for about five minutes. If the test is positive a crop of petechiae (pin-point hemorrhages) appears below the arm band and under it. The petechiae indicate an increased permeability of the capillary endothelium and are usually associated with a decreased number of platelets.

The increase of capillary permeability often associated with thrombocytopenic purpura has not been satisfactorily explained. Macfarlane<sup>23</sup> is of the opinion that the blood platelets, apart from their function as accelerators of coagulation and retraction, apparently have no important part in the production of maintenance of hemostasis. Howell<sup>21</sup> believes that in the normal individual the continuous disintegration of the circulating blood platelets in the capillaries may cause a localized coagulation of the plasma and that the fibrin formed thereby may serve to protect the integrity of the capillary endothelium. At any rate, it is obvious that before abnormal bleeding can occur there must be a capillary defect.

#### Sternal Puncture<sup>27</sup>

After the upper portion of the sternum, at the height of the second or third rib, has been prepared in the usual manner, the sternal needle (a modification of the needle devised by Klima and Rosegger) is forced directly into the bone marrow. One cubic centimeter of sternal marrow is aspirated into a dry syringe and placed immediately into a paraffin-lined tube containing a small amount of powdered heparin as an anticoagulant, the marrow fluid is transferred to a Wintrobe tube and centrifuged five minutes at 2000 r p m, the layers into which the marrow separates (erythrocytes, nucleated cells, plasma, and red and yellow fat) are recorded, the nucleated cell layer (erythroid, myeloid, megakaryocytic tissue, etc.) is mixed with an equal volume of plasma in a paraffin chamber. Counts and films of this nucleated

cell mixture are made. The films are made with an 18-mm. wide cover slip (same thickness as the counting chamber cover slip, but straight edged). The slide is air dried for several hours and stained with May-Grunwald-Giemsa or Wright stain, and studied microscopically for cell distribution and types. This procedure has been followed in more than 2375 bone marrow examinations.

#### Maturation of Megakaryocytes Bone Marrow Examination

The only consistent finding in thrombocytopenic purpura is a decrease in the number of circulating thrombocytes (plate-

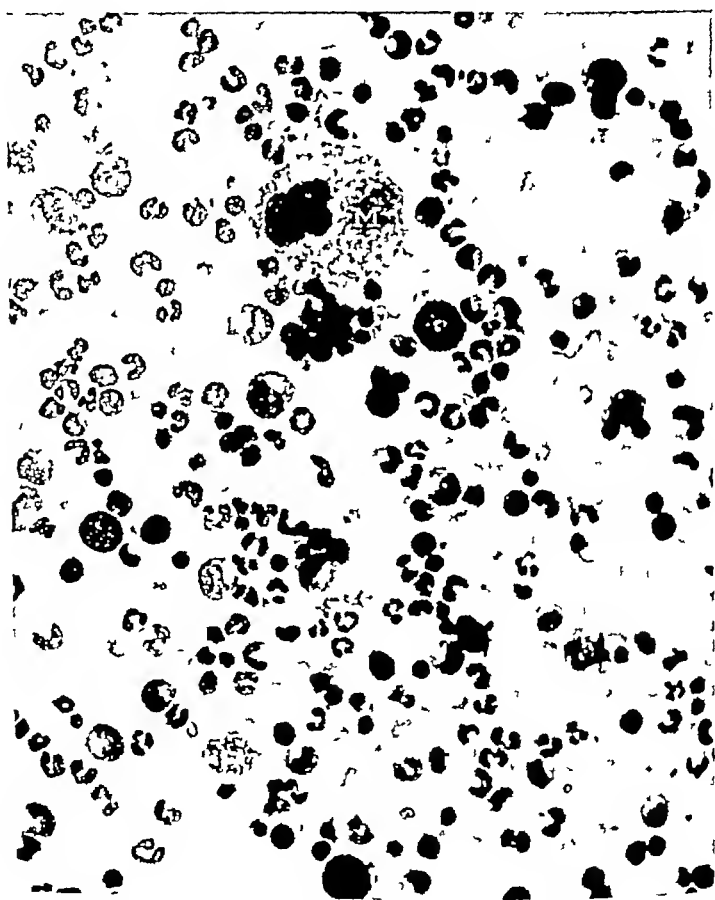


Fig 30—Normal bone marrow showing an adult megakaryocyte (M)

lets), therefore it is essential both diagnostically and prognostically to examine quantitatively and qualitatively the platelet-forming tissue, the *bone marrow megakaryocytes* (Figs 30-34).

The megakaryocytes are the largest cells in the bone marrow and are readily identified. The cells are classified as "young, adult and degenerated forms" Wright's<sup>57</sup> original observation that the megakaryocytes are the only source of true platelets has been repeatedly confirmed both clinically and experimentally by many investigators.<sup>1</sup> The earliest type of megakaryo-

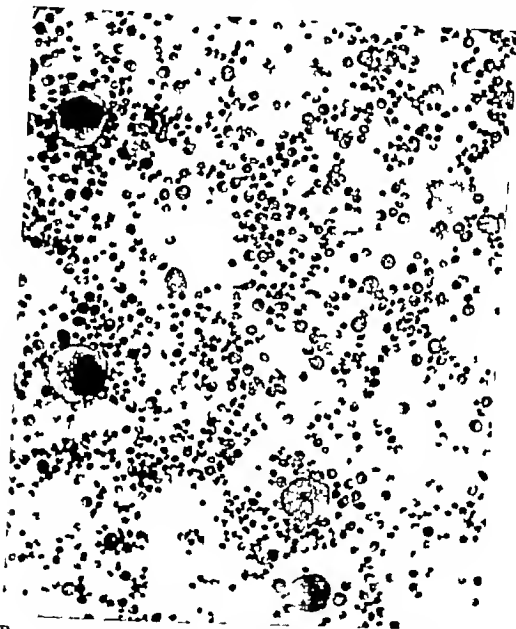


Fig 31—Bone marrow in a case of thrombocytopenic purpura showing immature type of megakaryocytic hyperplasia.

cyte (promegakaryocyte) has a number of morphologic characteristics similar to those of the myeloblast. Through a series of changes, first in the nucleus and later in the cytoplasm, the multilobulated adult (mature) megakaryocyte is formed (Fig 30). Megakaryocytes are formed occasionally by a series of complicated mitotic divisions of the nucleus without cell division. In the megakaryocyte the best criteria of maturity are the

amount, character and arrangement of the azurophilic granules in the cytoplasm. The number of lobes or the nuclear configuration is of little value in this respect. Immature megakaryocytes are usually smaller than mature megakaryocytes and contain a deeply basophilic cytoplasm. In degenerating megakaryocytes the giant nucleus shrinks and stains darkly, the cytoplasm dis-



Fig 32—Megakaryocyte showing platelet formation following splenectomy in a case of thrombocytopenic purpura

integrates and the final result is a naked, shrunken nuclear remnant. The formation of platelets occurs by a process of budding or by detachment of portions of the cytoplasm of the megakaryocytes in the bone marrow. It may also occur by cytolysis of the cytoplasm of these cells. The latter process is seen more frequently in aspirated human bone marrow. Mature mega-

karyocytes are formed from the myeloblast through a process of homoplastic hemopoiesis. Thus any disturbance involving the stem cell (myeloblast) will eventually interfere with the normal development of the megakaryocyte and this will result in quantitative and qualitative changes in these cells.



Fig. 33—Megakaryocytes from cases of thrombocytopenic purpura. *A*, *B* and *D* illustrate immature types of megakaryocytes and *C* is mitosis of a promegakaryocytes, *E* is an intermediate type of megakaryocytes and *F* is mitosis in a cell of the same type as *E*.

In essential thrombocytopenic purpura, in spite of the marked decrease in the number of platelets in the peripheral blood, a marked megakaryocytic hyperplasia is demonstrated in the bone marrow.<sup>11 28 46</sup> Young forms of megakaryocytes with single nuclei and relatively little or only moderately abundant cytoplasm and relatively few azurophilic granules are frequently

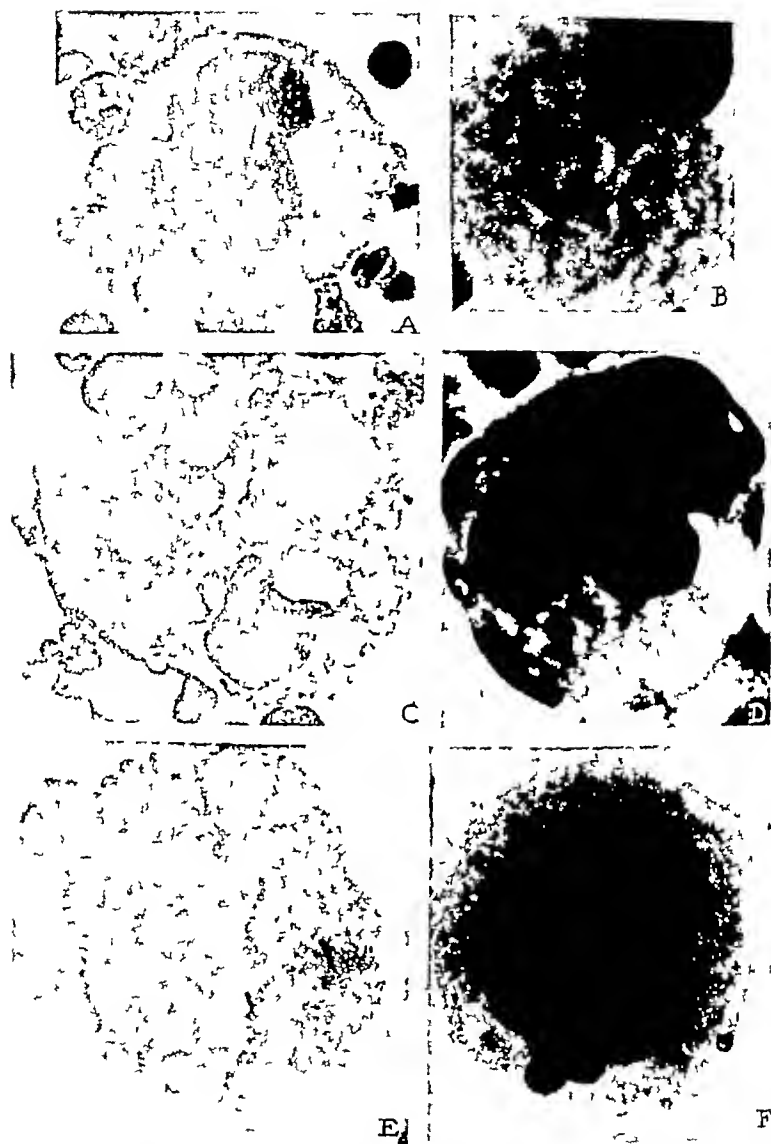


Fig 34—*A*, Hyaline megakaryocyte with azure-free cytoplasm in the bone marrow in a case of thrombocytopenic purpura *B*, Intermediate type of megakaryocyte showing extrusion of the nucleus in a case of thrombocytopenic purpura *C*, Toxic megakaryocyte in a case of thrombocytopenic purpura due to gold salts for the treatment of arthritis *D*, Degenerated megakaryocyte from normal bone marrow. *E*, Multipolar mitosis of a normal adult megakaryocyte *F*, Normal adult megakaryocyte showing the characteristic multilobulated nucleus and granular azurophilic cytoplasm

observed in the acute phase and to a less extent in the chronic phase of purpura haemorrhagica (Fig 31) Pathologic or "toxic" forms of megakaryocytes (Fig 34) such as lack of normal azuro-

philic granules,<sup>48</sup> vacuolization of the cytoplasm, small or large megakaryocytes with degenerative types of nuclei<sup>52</sup> and a hyaline cytoplasm and an absence of azurophilic granules are frequently observed in purpura haemorrhagica and in secondary thrombocytopenic purpura haemorrhagica—nephritis, gold salts, aplastic anemia, sulfonamide drugs, and so forth

#### Morphologic Changes in Platelets

Normally, platelets vary from 2 to 4 $\mu$  in diameter. They are spheric or ovoid granular bodies. When stained by Wright's stain, azure granules are seen in a hyaline, light blue cytoplasm. In the ordinary blood film they are seen isolated or clumped together. In thrombocytopenic purpura haemorrhagica, bizarre and pathologic forms of platelets and pseudoplatelets are observed in the peripheral blood. The latter forms are derived from the pathologic hyaline megakaryocytes in the bone marrow. Morphological changes are seen in the platelets such as giant forms, minute platelets and deeply stained ones. Rarely portions of the bone marrow megakaryocytes are seen in the peripheral blood.

#### ESSENTIAL THROMBOCYTOPENIC PURPURA (WERLHOF'S DISEASE<sup>53</sup>)

*Purpura haemorrhagica* is a condition of unknown etiology which is characterized clinically by spontaneous bleeding in the form of petechiae or ecchymoses into the skin, as well as hemorrhage from the mucous membranes and into the various organs. Petechiae are usually scattered over the arms, abdomen and legs and bleeding may occur from the nose, gums, and in some cases from the bowel, kidney and vagina. Intracranial hemorrhage is the most serious complication and may involve the brain, the spinal cord or the cerebrospinal meninges. Retinal hemorrhage is not unusual. In females there are usually disturbances in the menstrual cycle.

The first symptom of purpura haemorrhagica may be manifested by localized bleeding from the nose (epistaxis), bleeding gums, bleeding from the genito-urinary tract, profuse menstruation or menorrhagia or bleeding into the gastro-intestinal tract. Sooner or later purpuric lesions of the skin appear. These are minute, red hemorrhages which range in size from that of a pin point to that of a pinhead or slightly larger. Ecchymoses, large purple areas and even hematomas may occur.



Purpura haemorrhagica is a disease of childhood and young adults. It occurs more frequently in females than males. It is uncommon among Negroes. The disease has been reported during the first year of life and may even be present at birth in full-term and premature infants. A congenital type of the disease has been described. In 70 per cent of the author's series of forty-three cases the disease appeared before the age of twenty-four. The youngest patient was a female infant thirteen months of age and the oldest was a woman of fifty-five years. There were twenty-five females and eighteen males. The disease was observed in three female Negroes.

### Pathogenesis

The cause of essential thrombocytopenic purpura is not entirely clear. Much clinical and experimental work has been done and many theories have been advanced. No single theory for the cause of the disease adequately accounts for all the known facts relating to the disease. Frank<sup>15</sup> was of the opinion that the reduction in the number of circulating blood platelets and the morphologic changes of the megakaryocytes in the bone marrow was due to some noxa probably having its origin in the spleen. Minot<sup>35</sup> believes that the causative agent acts on the blood platelets, on the megakaryocytes or on the bone marrow as a whole. Kaznelson,<sup>26</sup> who first removed the spleen in a case of essential thrombocytopenic purpura, believed that the thrombocyte reduction in the peripheral blood was brought about by an increased thrombolytic activity of the spleen. The increase in the number of megakaryocytes in the bone marrow, in his opinion, was compensatory hyperplasia.<sup>25</sup>

Brill and Rosenthal<sup>4</sup> stated that the disease was associated with a disturbance in function of the capillary wall in addition to a disorder of the blood platelets. The changes in the capillary wall, they thought, were probably due to a reduction in the number of blood platelets. Wiseman, Doan and Wilson<sup>56</sup> support the theory of splenic cytolysis as the cause of the thrombocytopenia in this disease. Our studies<sup>28</sup> and those of others<sup>14</sup> support the view that the disease is due to a faulty maturation of the megakaryocytes in the bone marrow. Splenectomy removes a factor which is inhibitory to maturation. Some investigators attribute the megakaryocytic hyperplasia to the factor of bleeding, which is dependent on the severity of the disease.<sup>23</sup>

The function of the spleen in its relation to essential thrombocytopenic purpura is not definitely understood. It is usually regarded as the graveyard of both erythrocytes and thrombocytes. On the other hand, the depression of the megakaryocytes in the bone marrow was believed by Frank<sup>18</sup> to be due to some inhibitory splenic influence directed against the reticulo endothelial system from which the platelet-forming cells and granulocytes have their origin. Troland and Lee<sup>50</sup> report that extracts of spleens removed from patients with thrombocytopenic purpura contain a substance ("thrombocytopen") which, when injected into experimental animals will depress the blood platelets to a low level. Many investigators have failed to substantiate this work. Paul<sup>28</sup> studied the effect of intravenous injections of acetone splenic extracts from cases of essential thrombocytopenic purpura on the platelets and hemopoietic organs of rabbits. He noticed a transient significant depression of the platelet count in the peripheral blood of the rabbits, but there was no effect upon the number or cell structure of the megakaryocytes in the bone marrow. The spleen, liver and lungs of the rabbits showed no distinctive pathologic changes.

### Pathology

Except for the widespread hemorrhage, both gross and microscopic, which is a constant feature found in this disease at autopsy, and the finding of a megakaryocytic hyperplasia of the bone marrow there is little else of pathologic significance in thrombocytopenic purpura that is observed at necropsy. Studies on the spleens removed surgically, except for an occasional megakaryocyte, have failed to reveal any significant gross or histological abnormalities that would add any light to etiology of thrombocytopenic purpura.

### Clinical Manifestations

The symptoms and physical findings are variable because the disease may occur in both acute and chronic forms and further because of the tendency to relapses and remissions. The patients are more often observed during the relapse phase. A family history of ready bruising, frequent nosebleeds, profuse flow and irregularities in menstruation, excessive bleeding following small cuts or the extraction of a tooth, tonsillectomy and other operations or injuries are by no means unusual in these cases. The lymph nodes are not enlarged and the spleen is slightly palpable in less than one third of the cases. Large or massive spleens are

not observed in true cases of purpura haemorrhagica. In the chronic cases the condition of the patient is good.

In acute cases or during chronic phases of the disease with excessive bleeding the patient is pale because of the anemia. There may be a slight fever and a rapid pulse. Examination of the body may reveal a generalized distribution of petechiae and ecchymoses. The petechiae do not change on pressure. The hemorrhage areas vary from a dull red to yellow, purple and blue in color depending on their age. The signs and symptoms of hemiplegia or meningitis appear when intracranial hemorrhage takes place.

### Hematology

The characteristic blood finding is thrombocytopenia. The *platelets* are markedly reduced in number or even absent from the peripheral blood. In chronic cases the platelet count usually varies between 75,000 to 100,000 per cu. mm. although counts as low as 60,000 per cu. mm. are observed without obvious signs of bleeding. Sooner or later cases with such low platelet counts will present bleeding into the skin, either spontaneous or following the application of a tourniquet to the arm in order to obtain blood from a vein. The tourniquet test is strongly positive in practically all the cases during the active phase of the disease. During remission the test is often negative. Rarely may the platelet count be less than 50,000 per cu. mm. and the tourniquet is negative. If the skin over the vein is "flicked with the finger" while the tourniquet is still applied to the arm a crop of minute petechiae will gradually make their appearance. Usually bleeding does not occur unless the blood platelets are fewer than 60,000 per cu. mm. The chamber platelet count should always be checked with a blood smear that has been properly prepared and stained with Wright's stain. The blood platelets, besides being low, show morphological changes such as marked variation in size and abnormalities in shape.

The *bleeding time* is prolonged and the coagulation time is normal with a poor or absent clot retraction.

*Anemia*, if present, is usually normocytic in type. Severe and continued bleeding usually results in a microcytic hypochromic anemia. When bleeding has been excessive with erythrocyte counts as low as 1 to 1.5 million per cu. mm., the anemia is often macrocytic in type. Nucleated red cells are frequently

observed in the peripheral blood. Depending on the amount of bleeding a moderate to marked reticulocytosis is usually present.

The *leukocyte count* is usually normal. In cases with severe hemorrhage the count may be moderately elevated. Leukocyte counts as high as 20,000 with a moderate "shift to the left" to include an occasional neutrophilic myelocyte and metamyelocyte may occur. Leukopenia with a relative lymphocytosis in chronic cases has been described.<sup>40</sup> With secondary infections or following blood transfusions or where absorption products from suffusion or hematomas occur the polymorphonuclear neutrophils show varying degrees of "toxic" granulations in the cytoplasm.

The urine and stools may contain gross or occult blood. The blood calcium and fibrinogen and prothrombin time and cevitamic acid level of the blood are all within normal limits.

The *bone marrow examination* is the most important single differential diagnostic procedure. Symptomatic or secondary thrombocytopenic purpura such as occurs in leukemia, aplastic anemia, myeloma, leukosarcoma, pernicious anemia, Gaucher's disease, and "toxic" states are readily diagnosed and immediately separated from essential thrombocytopenic purpura. In acute thrombocytopenic purpura the bone marrow reveals a uniform stimulation with a myeloid, erythroid and *megakaryocytic hyperplasia*. In the more chronic cases without significant hemorrhage, the myeloid and erythroid hyperplasia may be absent, but the megakaryocytic hyperplasia persists. In the acute phase of the disease many of the megakaryocytes are of the young form and in the less acute and chronic phase of the disease most of the megakaryocytes are adult in type with an abundance of azurophilic granules in the cytoplasm. Some of the megakaryocytes reveal morphologic changes such as a hyaline cytoplasm and an absence of azurophilic granules. Degenerated or toxic forms of megakaryocytes with vacuolization of the cytoplasm are occasionally seen in primary purpura hemorrhagica, but are more frequently observed in greater numbers in some of the cases of symptomatic purpura hemorrhagica especially following infections and intoxications.

Following splenectomy the megakaryocytes qualitatively revert to normal, but quantitatively a moderate megakaryocytic, as well as myeloid and erythroid hyperplasia persists.

In my series of forty-three cases of thrombocytopenic pur-

pura a megakaryocytic hyperplasia was observed in forty. In two cases with an aplasia of the megakaryocytes one patient died following cerebral hemorrhage and the second died following splenectomy (Case VI). In a third case with a marked decrease in the number of bone marrow megakaryocytes, recovery occurred following a stormy postoperative course (Case VII).

## TREATMENT

### Medical Treatment

Untreated, the disease is often characterized by a cycle course of remissions and exacerbations. Temporary or apparent cures supposedly brought about through medical treatment, therefore, should be appraised with this fact in mind. In children less than ten years of age and in older individuals over forty years of age, thrombocytopenic purpura is usually mild in character and a spontaneous remission or one induced by medical treatment is usually complete and permanent. Only rarely is splenectomy indicated. Some investigators believe that the thrombocytopenic purpura of early infancy and childhood and that of adolescence and adult life are fundamentally different conditions. Clinically and hematologically there is little to support such a theory.

General treatment should include rest in bed, good nursing, and an appropriate diet. In general the diet should be liberal in animal proteins, fruits and green vegetables. Foods known for their value in furnishing hemoglobin-building materials, and for their vitamin content such as liver, chicken gizzard, kidney, eggs, apples, apricots, peaches, prunes, fresh lima beans, shredded wheat and puffed wheat, should be given in liberal amounts. For the anemia the administration of iron is indicated, such as ferrous sulfate 1 gm daily, reduced iron 3 gm daily or iron and ammonium citrate 6 gm daily. Preparations containing both iron and liver extract usually accelerate the rate of recovery.

Although *vitamin therapy* is not specific in thrombocytopenic purpura, since there is no evidence that lack of any of the synthesized vitamins including ascorbic acid is the cause of the disease, small amounts of some recognized multiple-vitamin preparation should be administered until the patient has recovered from the bleeding episode.

The *elimination from the diet* of foods to which the patient is allergic or sensitive has been suggested by the work of Squire and Madison.<sup>47</sup> According to these investigators, when patients

with thrombocytopenic purpura were placed on elimination diet the blood platelets returned to normal levels

The *removal of offending drugs* such as quinine, arsphenamine, benzene and sedormid which can act directly on the bone marrow megakaryocytes or cause depletion of the circulating blood platelets is an important precautionary measure, although these drugs are not the primary cause of thrombocytopenic purpura

During the phase of remission, *foci of infection* should be removed

*Snake venom* has been used both as a measure for controlling the bleeding and as a prognostic test For treatment from 0.4 to 1 cc and occasionally 2 cc of moccasin venom is given subcutaneously twice weekly Marked local reactions in the form of induced ecchymoses may occur Clinical improvement occurs without any definite improvement in the blood platelet level For the prognostic venom reaction, 0.1 to 0.2 cc. is injected intradermally A positive intracutaneous reaction occurs in practically all cases of purpura before venom treatment is started This intracutaneous reaction may persist in some cases but in other cases there may be a reversal from a positive to a negative reaction This persistence or reversal is said to be of value in determining the trend of the purpuric state According to Peck, Rosenthal and Erf,<sup>39</sup> patients treated with snake venom without reversal of the positive skin test to a negative one are likely to obtain little benefit from splenectomy We have had no experience with this test

There are a large group of *miscellaneous measures* and various remedies<sup>54-56</sup> which are of unproved value in the treatment of thrombocytopenic purpura The tendency for spontaneous improvement in this disease makes it difficult to evaluate their merits They include injections of foreign proteins, calcium, proprietary coagulants, epinephrine hydrochloride, viosterol, large doses of cevitamic acid, and other vitamins such as K, B<sub>2</sub> and A, liver extract, ventriculum, sesame oil, progynon, sulfuric acid, ergot, turpentine, anterior lobe of the pituitary, parathyroid extract, iodine and coal tar, snake venoms (tiger, moccasin) and antivenins (Bothrops), kephine hydrochloride, fat-soluble "T" factor and high protein diet.

Recently citrus pectin,<sup>22</sup> in the form of powder taken by mouth (capsules) in doses of 1 gm three times a day, one-half

to one hour before meals, has been reported to cause a cessation of bleeding without affecting the platelet level in cases of idiopathic thrombocytopenic purpura.

Foley has been able to induce remissions in two cases of thrombocytopenic purpura with marked vaginal bleeding as a prominent part of the hemorrhagic syndrome by the oral administration of stilbestrol in 5-mg doses every four to six hours for a period of two to three days

High voltage roentgen ray over the spleen or the exposure of patients with thrombocytopenic purpura to ultraviolet rays are of no definite therapeutic value

### Blood Transfusions

Where there has been much bleeding, blood transfusions are immediately indicated. The transfusions are repeated as often as necessary. Transfusions supply lost plasma volume and red blood cells, and the presence of platelets is useful in controlling the bleeding. Citrated blood given by the indirect technic is as effective as direct transfusions of whole blood in controlling excessive bleeding. The transfused blood platelets have little or no effect in reestablishing the normal blood platelet level and therefore should not be regarded as a curative measure. The blood transfusions serve to carry the patient along until a spontaneous remission sets in or as a preoperative measure in removal of the spleen.

Blood in amounts of 500 cc in the case of adult patients and in doses of 200 cc to 300 cc in the case of children should be given rather than several small transfusions. Injections of whole blood intramuscularly are not of any practical value. In cases of severe anemia due to marked loss of red blood cells, the use of concentrated red cell suspension (erythrocyte concentrates) will aid in restoring the normal circulating red cell volume. Rarely, intrasternal blood transfusions may be the only avenue of administration.

### Surgical Treatment

*Splenectomy* apparently results in a complete cure. Total cessation of bleeding in thrombocytopenic purpura in most cases occurs as soon as the splenic pedicle has been tied and before the platelets show any appreciable rise in the peripheral blood. Within twenty-four to forty-eight hours after splenectomy the

blood platelets reach a normal level (Fig 32) and in many instances the platelet level after several days may reach values of 500,000 per cu mm or more. I have observed one case in which the blood platelets following splenectomy reached a peak of 1,200,000 per cu mm in ten days. Eventually the blood platelets return to a normal level. In twenty cases of thrombocytopenic purpura observed by me following splenectomy the blood platelets promptly reached a normal level. In no instance was there a later fall to the original low levels of 50,000 or less and there was no reappearance of the bleeding diathesis.

Failures following splenectomy in some cases diagnosed thrombocytopenic purpura may be attributed to a number of factors: (1) incorrect diagnosis, (2) neglect of several important features before splenectomy is begun, such as the stage of the disease (acute or chronic phase) and the preoperative treatment, (3) the presence of accessory spleens,<sup>56</sup> (4) the postoperative treatment, and (5) the failure to examine the sternal marrow in order to determine the quantitative and qualitative status of the platelet-forming tissue, the megakaryocytes.

Splenectomy is of no value in symptomatic thrombocytopenic purpura. Splenectomy done in acute leukemia and aplastic anemia because of the bleeding tendency associated with a thrombocytopenia has been accompanied by disastrous results.

The operation should be performed by a skillful operator. Warren H. Cole in a late number of the *Surgical Clinics of North America*<sup>8</sup> has considered in detail the technic of splenectomy. Since splenectomy in acute phases carries a very serious risk,<sup>54</sup> energetic action is demanded to bring about a temporary remission through the liberal use of blood transfusions before the operation is begun. Not infrequently it will appear obvious, however, that cases of the acute incipient type, as well as the acute exacerbation of the chronic type, will result in a fatality unless splenectomy is performed. Death will result from external hemorrhage or from a sudden fatal termination through cerebral hemorrhage. If it appears that therapy has been ineffective, an emergency operation is indicated.

The care of the patient after operation has the same importance in the final outcome as preoperative therapy. The most important item in postoperative therapy is the administration of blood as transfusions and the transfusions are continued after splenectomy until the blood proteins and erythrocytes approach



normal or are appreciably raised. In general, all patients with anemia should have at least one transfusion postoperatively. In patients with severe anemia it may be necessary to give six or seven transfusions in as many days. This procedure will shorten the convalescence tremendously, and will minimize the amount of complications. Frequently, splenectomy is followed by an unexplained fever and tachycardia about twenty-four hours after operation. Cole believes that it is associated with a disturbance in the fluid and electrolytic balance, particularly the former. Treatment consists in an adjustment of the fluid intake, especially intravenous glucose and mineral electrolytes. The patients, following splenectomy, should be watched closely for hemorrhage from the splenic pedicle and for the early complications of pneumonia and atelectasis. Occasionally abdominal distention becomes very prominent. Less frequently an infection of the wound may develop. Symptomatic treatment of all complaints or complications and attention to minor details may be sufficient to alter the course from fatality to recovery.

The presence or absence of an adequate number of megakaryocytes in the bone marrow will decide between a good or poor result following splenectomy. Obviously a marked decrease or absence of platelet-forming cells (megakaryocytes) in the bone marrow contraindicates splenectomy. Many of the supposed failures with lack of platelet rise and the continuation of the abnormal tendency to bleed following splenectomy in thrombocytopenic purpura can be attributed to a failure to appreciate the diagnostic and prognostic value of bone marrow studies. In only two of the twenty-two cases of thrombocytopenic purpura subjected to splenectomy did the operation fail to bring about a normal platelet level in the peripheral blood, and a complete freedom from all the bleeding tendency (Cases VI and VII).

### Illustrative Cases

The following cases illustrate several of the more important features of thrombocytopenic purpura and the effect following the removal of the spleen.

**CASE I—*Essential Thrombocytopenic Purpura in a Boy***—P. H., a white boy, aged fifteen years, was admitted to the Illinois Research and Educational Hospitals on September 12, 1939, complain-

ing of epistaxis. Bleeding from the nose was first experienced in June, 1939, and was followed in a short time by persistent oozing of blood from the gums. Physical examination was essentially negative, except for numerous petechiae over the posterior aspect of the neck, cubital region, and chest. The spleen was not palpable. Blood studies on entrance showed platelets 40,000, erythrocytes 4,490,000, hemoglobin 13.0 gm., and a definite megakaryocytic increase of the sternal bone marrow. The bleeding time was twenty minutes and the coagulation time was nine minutes. The tourniquet test was positive. There was no clot retraction at the end of twenty-four hours.

The patient remained in the hospital under observation for several months. During this time he had many severe attacks of epistaxis. Platelet counts as low as 11,000 were obtained. Splenectomy was performed on December 21, 1939. The spleen weighed 290 gm. Six hours after removal of the spleen the platelets numbered 76,000, and eight days postoperatively a count of 980,000 was obtained. Several months later the blood platelets returned to a normal level. Bleeding subsided completely following splenectomy, and has continued so up to the present time.

*CASE II—Essential Thrombocytopenic Purpura in a Young Girl—*  
D. T., a white girl, aged fourteen years, was admitted to the Illinois Research and Educational Hospitals on March 10, 1938, complaining of frequent attacks of epistaxis and excessive menstrual bleeding. Bleeding from the nose was first noticed in October, 1937, at which time she experienced a nosebleed which persisted for two days. Menstrual period in November, 1937, continued for nine days, and in December, for fourteen days.

Physical examination was essentially negative, except for numerous petechiae, especially over both lower extremities. The spleen was not palpable. Blood studies on entrance showed platelets 48,000, erythrocytes 3,680,000, hemoglobin 8.5 gm., and a definite megakaryocytic increase of the sternal bone marrow. On March 19 the bleeding time was three minutes and the coagulation time was ten minutes. There was no clot retraction at the end of twenty-four hours and the tourniquet test was positive. Blood studies on March 25 showed platelets 61,000, erythrocytes, 2,930,000, hemoglobin 7.25 gm., and megakaryocytic hyperplasia of the sternal bone marrow.

Splenectomy was performed on April 11, 1938. The spleen weighed 157 gm. Twenty-four hours after operation the platelet count was 72,000. The platelets increased progressively, and on April 18 (seven days after splenectomy) they numbered 386,000. Following splenectomy there has been no bleeding at any time.

Thrombocytopenic purpura may be associated with various diseases such as hyperthyroidism,<sup>12</sup> catarrhal jaundice<sup>1</sup> and pulmonary tuberculosis. The association represents the incidence of two unrelated conditions. The same is true regarding the occurrence of purpura haemorrhagica in association with pregnancy.<sup>48</sup>

The following cases of thrombocytopenic purpura associated with pregnancy, hyperthyroidism and pulmonary tuberculosis illustrate the important features, course and treatment of two unrelated disorders occurring in the same patient.

*CASE III—Essential Thrombocytopenic Purpura Associated with Pregnancy*—B P, a white girl aged seventeen years, was admitted to the Illinois Research and Educational Hospitals on July 26, 1940. She had severe epistaxis, bleeding gums, purpuric spots, and bruised easily since December, 1938. At the time of entrance she was pregnant approximately seven months. Physical examination revealed red, spongy gums. The liver was palpable and tip of the spleen could be felt. The bleeding was controlled by blood transfusions and the patient was allowed to go into labor spontaneously on September 29, 1940. She delivered a normal full term baby girl that weighed approximately 6½ pounds. The puerperium was afebrile and uneventful.

Blood studies on her second admittance to the hospital showed platelets 100,000, erythrocytes 3,120,000, hemoglobin 9.8 gm., and a myeloid, erythroid and megakaryocytic hyperplasia of the sternal bone marrow. The bleeding time was twelve minutes, the coagulation time was nine minutes, and the beginning clot retraction occurred at the end of one and one-half hours. She was prepared for splenectomy by the administration of blood, and on October 23, 1940, the spleen was removed. The spleen weighed 203 gm. Twenty-three days postoperatively, blood studies revealed platelets 200,000, erythrocytes 5,910,000, and hemoglobin 17.5 gm. Since splenectomy there has been no bleeding from the nose or gums.

*CASE IV—Essential Thrombocytopenic Purpura Associated with Hyperthyroidism*—R V, a white woman aged twenty-two years, admitted to the Illinois Research and Educational Hospitals on June 24, 1938, had frequent attacks of epistaxis. Nasal hemorrhages commenced about February 15, 1938, and usually persisted for about one-half hour. She continued to have two or three hemorrhages weekly up until June 1, when the attacks became more frequent and prolonged. Menstrual history was normal until June

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12, 1938, and continued until July 1, with a marked increase in the bleeding

Physical examination revealed a moderate pallor of the skin and numerous bright red petechiae over chest, abdomen, back and extremities. The spleen was palpable and the tourniquet test was strongly positive. She also presented the symptoms and findings of exophthalmic goiter, including nervousness, irritability, tremor, palpitation, moderate weight loss and heat intolerance. The thyroid gland was bilaterally enlarged and soft in consistency. Exophthalmos was conspicuous. The basal metabolic rate was plus 33 per cent and the blood cholesterol was 143 mg per 100 cc. of blood.

Blood studies on entrance showed platelets 23,000, erythrocytes 2,300,000, hemoglobin 6.3 gm., and marked increase of the megakaryocytes on sternal bone marrow examination. The coagulation time was five minutes and the bleeding time was eight minutes. There was no clot retraction at the end of twenty-four hours.

Splenectomy was performed on June 30. The spleen weighed 270 gm. Five hours postoperatively there were 136,000 platelets with many large forms. Twenty-four hours after splenectomy platelets numbered 185,000, and on June 11 (eleven days after surgery) the platelet count was 473,000.

The patient was discharged from the hospital on July 24, with symptoms and signs due to bleeding disorder entirely cleared up, but the thyroid disease persisted.

She was again admitted to the hospital on November 11, 1938 with no change in the thyroid disorder. Blood studies at this time showed platelets 265,000, erythrocytes 4,150,000, and hemoglobin 11.5 gm. She was entirely cured of her thrombocytopenic purpura. She was prepared for surgery and a subtotal thyroidectomy was done on November 26. The postoperative course was uneventful and she left the hospital on December 1, 1938 in apparently good condition.

*CASE V—Essential Thrombocytopenic Purpura Associated with Pulmonary Tuberculosis*—E. L., a white boy aged thirteen years first entered the Illinois Research and Educational Hospitals on December 1, 1942, complaining of frequent and persistent attacks of epistaxis and bleeding from the gums. His mother stated that the boy had had nosebleeds since he was six weeks old. At first the nasal bleeding was slight and occurred once a month but the bleeding has gradually become more severe until the present time when it occurs at intervals of two weeks. He complained of a cough for the last two weeks.

Physical examination, except for a few dry, "squeaking" rales over the left lung anteriorly near the 2nd and 3rd ribs, was nega-

tive The spleen was not palpable, and the tourniquet test was negative Blood studies on entrance showed a platelet count of 20,000, erythrocytes 3,210,000, hemoglobin 60 gm, leukocytes 7100 with polymorphonuclear neutrophils 72 per cent, lymphocytes 21 per cent and monocytes 7 per cent The sedimentation rate of the erythrocytes (Wintrobe tube) was 33 mm in one hour The sternal bone marrow revealed a marked megakaryocytic, myeloid, and erythroid hyperplasia The bleeding time was eight minutes and the coagulation time was twenty-one minutes with no clot retraction at the end of thirty hours Roentgen examination of the lungs suggested bronchiectasis Several sputum specimens on examination revealed many acid-fast bacilli and the stomach washings also showed tubercle bacilli

Conservative treatment, including local treatment to nose and frequent blood transfusions, failed to stop the nasal bleeding which became more frequent and exhausting to the boy Splenectomy was finally performed on January 1, 1943 Five small accessory spleens were found, all of which were removed They were located in the pedicle, some of them lying against the pancreas The spleen weighed 310 gms Nasal bleeding stopped immediately following splenectomy, and he was given a number of blood transfusions postoperatively Blood studies on January 19, 1943, before his transfer to a tuberculosis institution, showed a platelet count of 460,000, erythrocytes 5,480,000, hemoglobin 160 gm, and leukocytes 14,100 The bone marrow revealed a moderate megakaryocytic hyperplasia

The finding of megakaryocytic hyperplasia in the bone marrow in thrombocytopenic purpura is essential before splenectomy In our experience an excellent result has followed splenectomy in all cases with a hyperplasia of the megakaryocytes In another group of acute and chronic thrombocytopenic purpuras a hypoplasia or aplasia of the megakaryocytes is observed Failure of improvement after splenectomy can be definitely correlated with the marked diminution or depletion of the megakaryocytes in the bone marrow

The following cases illustrate the course of events that may result when splenectomy is undertaken in a patient with aplasia of the megakaryocytes and in another instance where there is a marked diminution of megakaryocytes in the bone marrow

CASE VI—*Chronic Thrombocytopenic Purpura with Aplasia of the Bone Marrow Megakaryocytes*\*—D C, a white woman aged

\* This case was observed and studied with Doctor Albert VanderKloot, Chicago

thirty-three years, first entered the Illinois Research and Educational Hospitals on December 20, 1942, with generalized bleeding from the nose, gums, bladder, rectum, and into the skin and mucous membranes. She was in good health about four years ago when she had a miscarriage, following which she continued to have massive uterine hemorrhages which continued in spite of curettage and uterine packing. With the aid of numerous transfusions the bleeding subsided. She had had numerous subcutaneous hemorrhages following very minor blows or accidents for some months before this, but no particular attention was paid to them. For the past three years she had had a series of relapses with bleeding from the nose, gums, rectum and into the skin. The platelet count had been as low as 10,000, the erythrocytes decreased as low as 1,000,000, with a hemoglobin value of 16 per cent. She had been treated with iron, liver, blood transfusions, endocrine preparations, snake venom, calcium, pectin and large doses of vitamin C, following which there appeared to be temporary, but never a complete remission of the purpuric condition.

Physical examination revealed numerous and generalized petechiae distributed over the face, neck, chest, abdomen and both upper and lower extremities. There was profuse bleeding from the nose, gums and nasopharynx. Retinal hemorrhages were observed on examination of the eyegrounds. A hemorrhagic ulceration of the throat caused difficulty in swallowing. The spleen was not palpable and the tourniquet test was markedly positive. The bleeding times were over twenty minutes and the coagulation was ten minutes. There was no retraction of the clot at the end of thirty-six hours.

Blood studies on entrance showed a platelet count of 10,000, erythrocytes 2,680,000, hemoglobin 7.25 gm., leukocytes 3800 with polymorphonuclear neutrophils 42 per cent (many contained "toxic" granulations in the cytoplasm), lymphocytes 52 per cent, eosinophils 2 per cent and monocytes 4 per cent. No platelets were seen on blood smear examination. Repeated bone marrow examinations revealed a marked myeloid-erythroid hyperplasia with a markedly reduced number of megakaryocytes, almost a complete aplasia of these elements.

Splenectomy was performed on December 22, 1942. The spleen weighed 70 gm. Bleeding did not stop after removal of the spleen and marked bleeding from the bladder started shortly after the operation. Although she was given many blood transfusions she died of a cerebral hemorrhage on the twelfth day postoperatively. The blood platelets at no time reached a level of over 10,000 following splenectomy.

CASE VII—*Thrombocytopenic Purpura with a Marked Diminution of the Megakaryocytes in the Bone Marrow A Case of So-called "Uterine Thrombocytopenic Purpura."*—A E, a white woman aged twenty-two years, entered the Illinois Research and Educational Hospitals for the first time on March 10, 1940, complaining of profuse and continuous vaginal bleeding for the past eight weeks. She had received seventeen blood transfusions of 500 cc each before she entered the hospital. She was in good health until about two months ago, when she first began to have frequent attacks of epistaxis and bruised easily. The menstrual periods were very profuse and continued for six to seven days.

Physical examination on entrance into the hospital revealed a very pale individual with purpuric and ecchymotic areas on both arms, especially the right, and on the left thigh. There were petechial hemorrhages on the mucous membrane of the mouth, pharynx and buccal mucosa. Vaginal bleeding required change in her vaginal pad every two hours. The spleen was palpable two to three fingerbreadths below the left costal margin on deep inspiration. The tourniquet test was markedly positive. The bleeding time was ten minutes and the coagulation time was four minutes. There was no retraction of the clot at the end of twenty hours.

Blood studies on admittance showed a platelet count of 40,000, erythrocytes 1,118,000, hemoglobin 3.4 gm, leukocytes 16,450 with myeloid immaturity, reticulocytes 57 per cent, icterus index 3 units, and the mean corpuscular volume was 101 cubic microns. The bone marrow revealed a marked erythroid and myeloid hyperplasia with a marked diminution in the number of megakaryocytes.

Emergency splenectomy was performed on March 10 (late afternoon on day of admittance to hospital). The spleen weighed 415 gm, and a small accessory spleen near the splenic pedicle weighed 5 gm. The blood platelets gradually increased to 160,000 seven days after the operation. This was followed by a progressive drop in the platelets until they reached a level of 30,000 on April 18, 1940.

The vaginal bleeding continued and was exhausting to the patient in spite of frequent blood transfusions. On April 28, a series of roentgen ray treatments over the ovaries was begun. The vaginal bleeding gradually decreased in amount and finally stopped permanently. On August 16, 1940, the platelets numbered 80,000, erythrocytes 4,720,000, leukocytes 10,850 with a myeloid immaturity, reticulocytes 1 per cent and icterus index 7.5 units. The bleeding time was ten minutes and the coagulation time was nine minutes. There was a soft retractile clot at the end of twenty-four hours. The tourniquet test was still positive. The bone marrow

showed a myeloid and erythroid hyperplasia and definite increase in the number of normal appearing megakaryocytes.

The patient received approximately ninety-three blood transfusions of approximately 500 cc each while she was in the hospital. The blood studies October 23, 1940, showed blood platelets 210 000, erythrocytes 4,480,000, hemoglobin 12.25 gm and leukocytes 9650 with a normal differential count. The bleeding time and coagulation time were normal and the retraction of the clot occurred in two hours. The tourniquet test was negative. Bone marrow studies revealed many mature forms of megakaryocytes. She was free of the bleeding tendency. Except for a few symptoms due to the induced menopause, she has felt fine up to the present time.

### SYMPTOMATIC THROMBOCYTOPENIC PURPURA

The various causes of secondary or symptomatic thrombocytopenic purpura are listed in the classification given previously. The thrombocytopenia in the peripheral blood in many of these diseases may be associated with an aplasia, with a marked diminution, normal or increased number of bone marrow megakaryocytes.

In *aplastic anemia*, either the primary or secondary type, the hemoglobin, erythrocytes, leukocytes and platelets are usually uniformly reduced in the peripheral blood. There is a relative lymphocytosis and no signs of erythrocyte regeneration. Sternal marrow aspiration will show a hypoplasia of all the bone marrow elements. Secondary aplastic anemia is caused by chemical and physical agents such as x-rays and radio-active substances, or by systemic diseases such as nephritis, metastatic carcinoma, sarcoma, Hodgkin's disease (a rare cause of aplastic anemia) which either destroy or invade and replace (myelophthitic) the normal bone marrow elements. A careful clinical history, physical examination, laboratory data, detailed hematological studies, roentgenograms of the bones, lymph node and bone marrow biopsy many times will suggest the cause of the thrombocytopenic purpura. The same may be said of myelosclerosis.

*Pernicious anemia* and *chronic hypochromic anemia* may be associated with thrombocytopenia and purpura. The sore tongue, achlorhydria, microcytosis and normoblastic bone marrow, and in pernicious anemia the neurological symptoms, megalocytosis, bilirubinemia, megaloblastic type<sup>24</sup> of bone marrow and the



rapid response of the anemia and thrombocytopenia to adequate amounts of liver, should make the differential diagnosis simple

Splenomegaly associated with *Banti's syndrome*, *Felty's syndrome*, *thrombophlebitis of portal and splenic vein*, *idiopathic splenomegaly* and *cirrhosis of the liver* with secondary splenomegaly are more often observed with thrombocytopenia than with purpura<sup>30</sup> In many of these disorders besides the moderate reduction in the number of platelets, an anemia normocytic or macrocytic in type, leukopenia, neutropenia and a left toxic shift of the granulocytic series are frequent hematologic findings Esophageal varices demonstrated roentgenologically in splenic vein thrombosis, the late stage of Banti's symptom-complex and cirrhosis of the liver, and in Felty's syndrome the chronic deforming arthritis, or intermittently painful joints, cutaneous pigmentation and lymphadenopathy are findings of differential importance in this group of splenomegalic states The bone marrow reveals varying degrees of myeloid, erythroid and megakaryocytic hyperplasia depending upon the stage of the pathologic process Splenectomy is not specific, but with the exception of cirrhosis of the liver the removal of the spleen is followed by a marked clinical and hematological improvement

In *Gaucher's disease* thrombocytopenic purpura has been described a number of times<sup>3</sup> The classical findings are splenomegaly, pingueculae, skin pigmentation and the demonstration of the typical Gaucher cells by splenic or sternal puncture

A reduction in the number of blood platelets in association with petechial hemorrhages can occur in *erythroblastosis*, *sickle-cell anemia*, *hemolytic anemia* and *spherocytic jaundice* (congenital and acquired hemolytic icterus) These diseases can be readily differentiated from essential thrombocytopenic purpura by the clinical history, detailed studies of the blood and other appropriate laboratory procedures

In the *acute leukemias* and in the late phase of *chronic leukemia*, thrombocytopenic purpura is a common finding The leukemias can be readily diagnosed by observing in the peripheral blood immature types of leukocytes In doubtful cases with a leukopenia and very few "blast" cells in the peripheral blood, sternal puncture will show a hyperplasia of immature leukocytes, many of which are atypical forms There will be an aplasia of myelopoiesis and megakaryopoiesis

A platelet reduction on the basis of an *allergy* to certain

foods,<sup>47</sup> orris root, snake venoms, insect bite and pertussis vaccine has been reported. Whether the thrombocytopenia is due to the action of the substance directly on the bone marrow megakaryocytes or caused by a depletion of the circulating platelets is not definitely known. Beneficial results have been reported following the elimination of certain foods, such as wheat, potatoes and milk from the diet of allergic individuals with the symptoms of thrombocytopenic purpura.

Mild or severe purpura and thrombocytopenia may occur during the course of many acute and chronic *infections* (see previous tabulation). Fever, the lack of any evidence of previous hemorrhagic tendencies, blood cultures and blood agglutination tests, blood Wassermann reaction, roentgenological examination of the lungs and throat and sputum examination are a few of the tests that will readily separate the infectious states from essential thrombocytopenic purpura. The bone marrow in practically all of the infections reveals a marked myeloid hyperplasia with a moderate or marked toxic granulopoietic tissue.

Purpura and thrombocytopenia have been repeatedly observed following the administration or contact with a number of *chemicals and drugs* (see tabulation). The granulocytes and erythrocytes may not be affected, although continued action of the chemical on the bone marrow may result in disturbances of granulopoiesis and erythropoiesis with a resulting anemia, leukopenia and thrombocytopenia in the peripheral blood. The *organic arsenicals*<sup>8</sup> are the best known causes of thrombocytopenic purpura by their toxic effects on the bone marrow megakaryocytes. *Gold salts*, benzol and sedormid<sup>10</sup> may also produce a purpura. I have seen one case of severe, fatal thrombocytopenic purpura following the administration of gold salts for the treatment of arthritis. The bone marrow megakaryocytes showed marked toxic and degenerative changes involving the nucleus and cytoplasm with lack of platelet formation.

Secondary thrombocytopenic purpura following the use of *sulfonamide drugs*<sup>10</sup> has been reported in a number of cases, with death in several of them. The amount of drug necessary to produce purpura is extremely variable. The author observed one case in which a patient was given six tablets of sulfanilamide daily for one week for undulant fever before purpura developed. The bone marrow megakaryocytes were quantita-

tively and qualitatively normal, although the platelet count was less than 50,000. She died of a cerebral hemorrhage.

Thrombocytopenic purpura is rarely caused by *organic hair dyes*<sup>2</sup> and *leg stocking color preparations*. Sloan<sup>45</sup> has observed two cases of thrombocytopenic purpura following the use of commercial leg stocking color preparations. In one of these cases studied by me the bone marrow showed a marked diminution in the number of megakaryocytes, while the myeloid and erythroid cells appeared normal.

*Congenital* thrombocytopenic purpura has been reported in the literature several times. Whitney and Barritt<sup>51</sup> reported its occurrence in two children of the same mother as a result of two consecutive pregnancies.

#### DIFFERENTIAL DIAGNOSIS

Thrombocytopenic purpura should be distinguished from nonthrombocytopenic purpura, hemophilia, hereditary hemorrhagic thrombasthenia,<sup>17</sup> familial epistaxis,<sup>18</sup> hereditary fibrinogenopenia,<sup>34</sup> and hemorrhagic telangiectasia.<sup>37</sup>

*Nonthrombocytopenic purpura* occurs in anaphylactoid or allergic conditions, such as *Schönlein-Henoch disease* and *erythema of Osler*, which are characterized by the clinical symptoms of allergy such as erythema, urticaria or effusions of serum into subcutaneous or submucous tissues or viscera. These conditions are mainly the result of increased capillary permeability which allows the passage of plasma and the cellular elements of the blood. There may be a polymorphonuclear leukocytosis and an eosinophilia. The blood platelets, bleeding time, coagulation time and clot retraction are normal. The tourniquet test may be positive or negative. The bone marrow megakaryocytes are not affected.

Many *infections* such as scarlet fever,<sup>33</sup> typhoid fever, subacute bacterial endocarditis, influenza, diphtheria, scarlet fever and septicemias due to various organisms more often produce a purpura without thrombocytopenia. The purpura is either the result of emboli or due to capillary damage produced by toxins.

The nonthrombocytopenic purpura that results from use of *chemicals and drugs* is probably the result of idiosyncrasy. Snake venoms, due to their injury to the endothelial lining of the capillaries, produce multiple hemorrhagic lesions anywhere in the body.

The presence of adequate amounts of ascorbic acid in the body is essential for the proper formation of the "cement substance" between the endothelial cells of the capillary wall. A deficiency of ascorbic acid may result in purpura not associated with a platelet reduction in the peripheral blood.

A miscellaneous group of purpura unassociated with any primary abnormalities of the blood-forming organs include *purpura simplex*, *purpura fulminans*, *purpura senilis* and *purpura cachectica*, *mechanical purpura*, *orthostatic purpura* and *David's disease* which is considered the result of ovarian hormone deficiency.

In *hemophilia* the prothrombin is normal even though the clotting time is prolonged. This is due to the fact that in this disease the platelets are abnormally resistant and therefore yield thromboplastin too slowly to bring about coagulation within the normal time. The clot retraction and blood platelets, as well as the formed elements of the blood, are normal. Anemia, when present, results from excessive bleeding.

*Vitamin K deficiency*<sup>5</sup> or absence of fibrinogen may cause excessive bleeding with prolongation of both bleeding and coagulation times.

In *hereditary hemorrhagic thrombasthenia*, a type of non-thrombocytopenic hemorrhagic disorder due to defective platelet function, the bleeding time is increased, clot retraction delayed and tourniquet test positive, whereas coagulation time is normal. Purpura is unusual in this disease.

In *familial epistaxis* both the bleeding and coagulation time are normal. Local or generalized abnormalities are not discernible.

In *hereditary hemorrhagic telangiectasia* bleeding may come from telangiectases in any location, although epistaxis is especially common. The anemia results from blood loss and the bleeding time, coagulation time, clot retraction and platelet count are normal.

*Polycythemia vera*, *erythroleukemia* and *primary thrombocythemia*<sup>12</sup> associated with bleeding tendencies and purpura reveal a normal or more often an increased platelet count, excessive production of erythrocytes, leukocytosis with a normal, leukemic, or leukemoid blood pattern, and a normal bleeding and coagulation time.

*Lupus erythematosus disseminatus* occasionally is associated

with thrombocytopenic purpura In two cases which I observed the bone marrow showed erythroid, myeloid and megakaryocytic hypoplasia which was reflected in the peripheral blood by anemia, leukopenia and thrombocytopenia

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## THE TREATMENT OF LEUKEMIA\*

HOWARD L. ALT MD†

LEUKEMIA was first described as a clinical entity in 1845. Since that time much knowledge has accumulated concerning the nature of the disease but the cause and a specific treatment remain obscure. Fortunately, leukemia is not a common disease. In Denmark, the yearly total number of deaths is 1 per 50,000 of population. A single physician then would be expected to see few cases during a lifetime of practice.

Leukemia is conveniently classified according to the cells involved, the most common types being myelocytic, lymphocytic and monocytic. It may be further broken down into the acute, subacute and chronic forms. The acute fulminating cases differ sufficiently from the subacute milder cases to warrant this subdivision. The treatment of leukemia is guided almost entirely by whether the disease is acute, subacute or chronic. The cell type is of secondary importance.

A great variety of agents has been used in the treatment of leukemia with varying success in alleviating symptoms and signs. The most important and useful of these are irradiation, arsenic and blood transfusions. To use these agents to the greatest advantage, the individual case must be carefully classified as to the type and the stage of the disease. The management of the patient then continues for the rest of his life. A constant check of the blood picture and the clinical condition is necessary to guide therapy intelligently.

As with other diseases in which a cure has not been established, there is no uniform method of treating leukemia at the present time. Authorities differ greatly in their opinions as to the use of irradiation, arsenic and blood transfusions in various types of cases. The purpose of the present paper is to outline a plan

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\* From the Department of Medicine Northwestern University Medical School, and from the Passavant Memorial Hospital Chicago.

† Assistant Professor of Medicine, Northwestern University Medical School. Attending Physician, Passavant Memorial Hospital.



of treatment of leukemia that has given the author the most satisfactory results over a period of years

In discussing the diagnosis and treatment of leukemia, emphasis will be placed on typical, well defined types of the disease. Actually there are tremendous variations in the symptomatology, course and response to treatment in cases that are classified in the same general group. It is sometimes necessary to follow the course of the disease for some time before the prognosis and the effects of treatment can be determined.

### ACUTE LEUKEMIA

Cases are classified as acute leukemia when the onset is rather rapid with high fever and the picture of acute sepsis. There is swelling and inflammation of the gums and the spleen is usually palpable. Adenopathy is common, especially of the cervical group. If the disease is seen very early, there may be little anemia or thrombopenia, but in the course of a few days a progressive decline of the erythrocyte count and platelet count will be noted. As the platelets decrease, there are hemorrhages from the mucous membranes and ecchymoses and petechiae in the skin. The white blood count varies within wide limits, but usually is moderately elevated (25,000 or 50,000 per cu mm). On the blood film, a high percentage of blast cells will be seen. In most cases the cell type can be determined from the more mature leukocytes present, but in some in which most of the cells are in the blast stage the diagnosis of acute leukoblastic or stem cell leukemia must be made. The course may be extremely rapid in these cases. An adult male during a mild respiratory infection had a normal leukocyte and differential count. In a few days he developed the typical picture of acute myelocytic leukemia. The condition grew progressively worse and he expired ten days after the original count was made. Another patient lived only two weeks after the initial symptoms of acute leukemia began. Although the course of the disease is not usually this rapid, it is uncommon for these patients to live more than one to two months.

*Treatment* has little or no effect on the course of acute leukemia. Irradiation or Fowler's solution are not only of no benefit, but are actually harmful. After such treatment there may be an increase in fever and a more rapid decline in the erythrocyte and platelet count. Blood transfusions cause a transient rise in

the red cell count but the effects are only apparent for a few days. Their use does not warrant the time and expense involved. Any treatment for acute leukemia will only be a gesture for the satisfaction of the patient and his relatives.

#### SUBACUTE LEUKEMIA

Although acute leukemia, as described above, may merge into the subacute variety, the latter on the whole is much more benign and presents a rather different picture. It occurs in all age groups. The patient with subacute leukemia is frequently ambulatory when first seen for symptoms of weakness, easy fatigue, pallor and afternoon fever of one or two months' duration. A history of spontaneous bruising of the skin is frequently elicited. As often as not, there is no lymphadenopathy and the spleen is not palpable. When present, the enlargement of the lymph glands and/or the spleen is usually slight.

The prominent feature of the blood picture in these cases is the rather marked anemia which may be of the macrocytic type. The erythrocyte counts will be in the range of 1 to 3 million per cu mm. Contrary to the usual conception, leukocytosis is not a constant feature in subacute leukemia. In over half of the cases, the count will be under 10,000 per cu mm and leukopenia is common. A careful differential count practically always reveals a varying percentage of blast cells, which are classified according to the more mature cells present. Complete absence of immature cells in the peripheral blood in subacute leukemia is rare. Lastly, the platelet count is markedly reduced, usually to below 50,000 or 75,000 per cu mm. At times it may be difficult to differentiate subacute leukemia from aplastic anemia. If there is any doubt about the diagnosis, a sternal puncture should be performed. In leukemia the marrow will be found to be hypercellular and contain a high percentage of blast cells. The course and treatment are quite similar whether the disease be of the myelocytic, lymphocytic or the monocytic type.

As the disease progresses there is a continuous fall in the erythrocyte count not unlike that seen in patients with aplastic anemia. The fever increases and there is progressive weakness and loss of weight. Hemorrhagic phenomena secondary to the thrombopenia occur. These patients often have a steady oozing of blood from the gums. Toward the end, patients who have not had a leukocytosis or splenomegaly earlier may have a rapidly

progressive enlargement of the spleen and a sharp increase in the leukocyte count to over a hundred thousand. The average life expectancy in subacute leukemia is four to eight months but since practically all patients receive blood transfusions, the course may be shorter without this treatment.

*X-ray therapy* has been given a thorough trial in the treatment of subacute leukemia. Almost without exception, there is no benefit or the disease is made worse. The leukocyte count can be reduced with roentgen therapy but there is also a depression of the erythrocyte and platelet counts. One possible beneficial effect of x-ray in subacute leukemia is for the treatment of a local leukemic tumor. An elderly woman with subacute monocytic leukemia had a tumor mass in the nasopharynx which completely obstructed the nasal passages. Local irradiation caused rapid shrinking of the tumor but had no effect on the general disease. Radio-active phosphorus is also without effect in the treatment of subacute leukemia. This might be expected as it is a form of irradiation and does not act very differently from x-rays.

No benefits have been observed from *medicinal therapy* in subacute leukemia. Arsenic in the form of Fowler's solution is contraindicated as it might further inhibit the formation of erythrocytes and thrombocytes. Liver and iron preparations have no effect on the severe anemia. Repeated injections of liver extract might conceivably stimulate myelopoiesis and should therefore not be given to excess, especially in myelocytic leukemia. Vitamins are likewise without effect.

### Blood Transfusions

The only treatment that has any real effect on the patient with subacute leukemia is blood transfusion. To be sure, the effect is temporary but any treatment that will improve the patient's feeling of well-being, allow him to be more active, and possibly prolong his life is distinctly worth while. One may wait until the erythrocyte count falls below 2 million per cu mm and the hemoglobin below 6 gm per 100 cc before giving blood. With a count above this level the average patient can be moderately active without symptoms due to anoxemia. Because of the severity of the anemia, it is best to give large transfusions. The donor can spare 100 cc blood per 25 pounds of body weight without the occurrence of untoward symptoms.

The adult patient with leukemia would then receive 600 to 700 cc blood in a single transfusion. Citrated blood has been used in all cases.

Striking effects are noted after a blood transfusion in the early stages of subacute leukemia. The symptoms of fatigue and weakness, which are similar to those seen in toxemia, are markedly improved. If oozing from the gums is present, this is temporarily controlled. A decrease in the size of the spleen was observed in one patient who had slight splenomegaly. The slight to moderate fever is practically always reduced and at times returns to normal for varying periods. Within twelve to twenty-four hours after the transfusion, a considerable reduction in the leukocyte count has been observed and this occurs mostly at the expense of the blast cells. Counts originally of 10,000 to 12,000 per cu mm have decreased to 3000 to 4000 and counts over 20,000 have decreased to less than half the original value. It is unlikely that the above effects are related to the small increase in the erythrocyte count averaging about 500,000 cells per cu mm. It almost seems that there is something in whole blood that temporarily counteracts the leukemic process.

After one to three weeks, depending on the type of the case and the stage of the disease, there is a gradual return of the previous symptoms and signs. In most cases, the erythrocyte count which gradually decreases is used as an index for further transfusions. The patient then leads a "transfusion life" much as does the patient with aplastic anemia. As time goes on, blood transfusions have less and less effect, and are of no value when the patient finally goes into the acute terminal stage.

Occasionally, temporary and partial remissions occur during the course of subacute leukemia. During these times it may be possible to go several months without transfusions. Some of the beneficial effects reported with the use of various agents such as bone marrow or urine extracts may well be related to the simultaneous use of blood transfusions and the occurrence of remissions.

A troublesome feature in leukemic patients who receive multiple transfusions is the occurrence of febrile reactions. No means have been found of preventing such reactions. However, the reactions are seldom hemolytic in nature and the effects seem to be about the same whether reactions occur or not.

The following cases of subacute leukemia illustrate the beneficial effects of blood transfusion

**CASE I**—A man, aged sixty-two years, was seen in September, 1938, with the complaint of weakness and pallor. The physical examination was essentially negative. The blood picture was as follows: erythrocyte count 1 million per cu mm, platelet count 60,000 per cu mm, leukocyte count 9200, differential—immaturity of the myeloid series. A sternal puncture confirmed the diagnosis of subacute myelocytic leukemia. A series of blood transfusions raised the erythrocyte count to over 3 million per cu mm and he felt practically well. Thereafter because of progressive anemia, he received transfusions of 600 cc blood first at about three-week intervals and later at intervals of ten to fourteen days. He spent several months in Florida during the winter and was able to go away for several weeks the following summer. In October, 1940, over a year later, the spleen became enlarged, the leukocyte count rose rapidly and he died within a few weeks. Over fifty transfusions were given in the course of the illness, during which time he was able to lead a moderately active life.

**CASE II**—A diagnosis of subacute lymphocytic leukemia was made in a ten-year-old girl in June, 1939. The erythrocyte count was 1.3 million per cu mm, the white blood count was 32,000 with a high percentage of lymphocytes and lymphoblasts, and the platelet count was reduced below 50,000 per cu mm. There was moderate fever and the spleen was palpable. Blood transfusions caused a marked improvement and during the following six months the leukocyte count averaged below 10,000 per cu mm. A gradual increase in symptoms and signs always occurred as the effects of the transfusions wore off. However, the patient remained well enough to attend school the following fall. Symptoms progressed rapidly in December, 1939, and she died a month later.

Many other cases have shown similar results with blood transfusions.

It is difficult to prove that life is prolonged by repeated transfusions, as no control group is available for comparison. Even though many authors are not enthusiastic about blood transfusions in subacute leukemia, the progressive anemia which is so constant is practically always treated by this means. Without transfusions it is quite possible that death would occur earlier. One can say with certainty that the transfused patient feels

much better and is often able to lead an active life for a fair period of time

Economic difficulties frequently arise when numerous blood transfusions are given. In recent months, it has become common to give *red cell suspensions* from which the plasma has been withdrawn, as a substitute for whole blood in the treatment of anemia. As the expense and trouble involved is much less than with whole blood, it is practical to give large quantities of cells over a short period of time. It is also practical to give the patient red cell suspension transfusions at the office or outpatient department. One patient with a subacute monocytic leukemia has been given several transfusions of red cell suspension of 1000 cc each which is the amount obtained from 2 liters of blood. She felt greatly improved, the anticipated rise in erythrocyte count occurred and there was a reduction in the low grade afternoon fever. It is not yet possible to say whether red cell suspensions will have the same beneficial effects as whole blood in the treatment of subacute leukemia.

#### Management of the Patient and His Family

There are few patients who try the tact and patience of the physician more than the one with subacute leukemia. It is difficult for the relatives to understand that their loved one, not infrequently a young adult or child who appears in comparatively good health, has not more than six to eight months' life expectancy. The more intelligent and critical relatives will stop at nothing to determine whether someone else has more to offer than their doctor. After exhausting the possibilities in their own community, they often consult specialists and large medical clinics throughout the country. The greatest hope that can be offered is that a cure for the disease might be discovered while the patient's life is being prolonged by blood transfusions.

How much the patient should be told about the nature of his condition depends largely on the individual case. In most instances, it will be better to tell him little. The patient with subacute leukemia should be encouraged to lead as normal a life as possible without producing disagreeable symptoms. It is surprising how much the average patient can do even though he has a rather marked anemia and a moderate fever. The mere fact that he is allowed to lead an active life will give him hope and encouragement for the future.

## CHRONIC MYELOCYTIC LEUKEMIA

The clinical picture of chronic myelocytic leukemia is more clearly defined than subacute leukemia and is therefore more familiar to physicians. It is possible that the etiology is different from the acute forms of leukemia. The patient consults the physician because of a feeling of weakness or because of a sense of discomfort in the region of the spleen. Not uncommonly the condition is recognized in the course of a routine leukocyte count. Examination reveals enlargement of the spleen, the size depending on the duration of the disease. The erythrocyte count averages 3 to 4 million per cu mm, the leukocyte count is increased usually to over 100,000 and the platelets are normal or increased in number. The differential count shows a varying percentage of promyelocytes, myelocytes and metamyelocytes.

## Roentgen Ray Therapy

Roentgen irradiation has held the most important place in the treatment of chronic myelocytic leukemia since it was used successfully by Senn in 1904. A great number of different techniques have been employed. Earlier it was the custom to give rather large doses of x-rays at frequent intervals. These were given over small areas, the most common sites being the spleen, long bones and chest. Reactions were common and a marked leukopenia sometimes occurred. More recently, smaller doses of x-rays have been favored by most roentgenologists. In 1931, Teschendorf observed good results with the use of *irradiation of the whole body*, so-called "spray" or teleroentgentherapy. Since then, this method has been used by many others and with considerable success. As the leukemic process is widely dispersed in the body, it would seem more logical to treat the patient generally rather than locally. In our clinic, irradiation of the whole body with the exception of the head and genitalia has been used for the treatment of chronic leukemia since 1937. The factors are: voltage 220, milliamperes 20, distance 6 feet, filter 0.5 mm copper plus 1 mm aluminum, time for exposure with equipment used 11 minutes, roentgens 35. The patient is placed across the room from the tube and treatments are given alternately to the front and back of the body. There is rarely any reaction with the dose of 35 roentgens. If a reaction does occur, the dose for subsequent treatments is reduced to 30 roentgens.

A common method of application of x-rays in leukemia is to treat the patient intensively and then to wait for a relapse to occur before giving further treatment. The leukocyte count is usually considered to be less important than other symptoms and signs in determining when treatment is to be reinstituted. This general plan of treatment appears illogical. As the patient with chronic leukemia feels best when the leukocyte count is low and the spleen relatively small, every attempt should be made to maintain this state as continuously as possible. At first the patient is given total body irradiation at weekly intervals until the leukocyte count falls to the range of 10,000 to 15,000 per cu. mm. It should be remembered that the leukocyte count continues to decrease for a week or longer after each irradiation. Following treatment there will be a marked improvement in strength, the spleen decreases in size until it may be no longer palpable, and the erythrocyte count increases by 500,000 to 1 million cells per cu. mm. In this state, the patient may feel perfectly well and should be encouraged to live a normal existence. Subsequently a leukocyte count is made every two to 4 weeks and the size of the spleen recorded in fingerbreadths below the costal margin. As the leukocytes increase to over 15,000 or 20,000 per cu. mm and a slight increase in the size of the spleen occurs, another treatment is given. The intervals between x-ray treatments depends largely on the individual case. Some patients can be maintained in a fair state of remission with treatments every two to three months, whereas others require them more often. This so-called continuous treatment of leukemia was advocated by Murphy in 1940.

#### Radio-active Phosphorus

A new method of irradiation which has been in use for three years and shows great promise is radio-active phosphorus. Its advantage over x-rays is that it can be given orally, there are no reactions, it is specifically absorbed by the leukemic cells and it has a continuous action for over fourteen days. Lawrence and his co-workers have observed prolonged remissions in chronic leukemia with the repeated administration of radio-active phosphorus. Unfortunately, this substance is not available for general use at the present time. It would seem that the continuous treatment with total irradiation described above is an approach to the principle of treatment with radio-active phosphorus.



### Arsenic Therapy

An adjunct to irradiation in the treatment of chronic myelocytic leukemia is solution of potassium arsenite (Fowler's solution) After being almost forgotten for many years, Forkner and Scott revived interest in arsenic in 1931 They demonstrated an effect similar to that of irradiation in patients with chronic myelocytic leukemia. The disadvantages of Fowler's solution are the frequent occurrence of toxic symptoms, such as weakness, anorexia, nausea and vomiting, diarrhea and herpes zoster and the fact that a relapse may occur even while treatment is continued It has been found that significant toxic symptoms can be largely avoided if Fowler's solution is given in smaller doses and over a shorter period of time than recommended by Forkner and Scott. The method has been to give 3 minims three times daily the first day and to increase the dose one minim each day up to 10 or 12 minims three times daily At the first indication of toxicity, the drug is omitted for one day and then resumed at a dose one minim less than that which caused the reaction This dose is continued through a period of twenty-one days from the time the arsenic was first given This amount of treatment will usually cause an appreciable drop in the leukocyte count and a decrease in the size of spleen, the maximum effect occurring about seven to ten days after treatment, is stopped In order to avoid any cumulative effects, a rest period of six weeks is allowed before another course of the drug is given

### Arsenic and Roentgen Therapy Alternately

To maintain a continuous remission, it has been found very satisfactory to alternate arsenic therapy with roentgen therapy Fowler's solution is given for a period of three weeks as outlined above If in the six weeks following, the leukocyte count rises above 15,000 per cu mm., one or more total irradiation treatments are given Thus the patient remains in remission and avoids the expense and trouble of taking as many x-ray treatments as otherwise would be required One patient with chronic myelocytic leukemia received alternating arsenic and x-ray therapy over a period of five years He worked the entire time and for the most part enjoyed excellent health His disease was always easier to control during the summer months at which time he worked outside in the sun During these times it was

often unnecessary to give roentgen therapy between the courses of Fowler's solution. The beneficial effect of sunlight was also noted by Poole and his associates in 1938.

#### Terminal Stage, Duration of Life

In all patients with chronic myelocytic leukemia there comes a time when x-ray and arsenic treatment is no longer effective and may even be harmful. The turning point may become apparent within the course of a few weeks and is characterized by weakness, fever, a decline in the erythrocytes and platelets, and an increasing number of myeloblasts in the blood film. After these signs appear, the life expectancy is not more than a few months at most. This terminal stage of the disease should not be confused with the acute picture that is sometimes seen in the chronic stage, as illustrated in the following case.

**CASE III**—A male, aged twenty-two years, was seen who had had symptoms of leukemia for over a year but had never received Roentgen therapy. He was emaciated and had a high fever. His spleen filled the entire left half of the abdomen. The erythrocyte count was 2 million per cu mm and the leukocyte count 2.5 million per cu mm. The blood film showed a great preponderance of promyelocytes but relatively few myeloblasts. The platelets appeared normal in number. His physician and roentgenologist felt that x-ray therapy was contraindicated because of the acuteness of the condition. As the blood picture was compatible with the chronic stage of myelocytic leukemia, however, a series of x-ray treatments were given. The leukocyte count returned to normal, the spleen decreased greatly in size and he was able to be ambulatory in a few weeks. Death occurred one year later.

The average duration of life in chronic myelocytic leukemia is said to be about three to four years but many patients live much longer. It is the consensus that life is not significantly prolonged by the use of roentgen or arsenic therapy. One wonders how accurate are these statistics. In a small series of patients who were given "continuous" total irradiation therapy, Murphy felt that life was prolonged greater than in another series treated by the interval massive dose technic. Regardless of whether life is or is not prolonged, the maintenance of these patients in a state of relatively good health and economic efficiency justifies the treatment given.

## CHRONIC LYMPHOCYTIC LEUKEMIA

The clinical picture and course of chronic lymphocytic leukemia resemble the myelocytic type. The disease occurs preponderantly in individuals over forty-five years of age. Although the life expectancy is said to be about three and one-half years, the cases on the whole have run a more benign course in the lymphocytic group. The diagnosis of chronic lymphocytic leukemia is not infrequently made during a routine examination. In the earlier stages, there is slight to moderate enlargement of the lymph glands, spleen and liver. The leukocyte count is usually over 100,000 and about 90 per cent of the cells are mature lymphocytes. Slight reduction of the erythrocyte and platelet counts is common.

In the last few years, several cases have been recognized at a very early stage. The only positive findings were leukocyte counts between 25,000 and 35,000 per cu mm and a high percentage of lymphocytes in the blood film. No treatment is indicated in this phase of the disease, which may continue for some time.

In the more advanced cases, with lymphadenopathy, splenomegaly and leukocyte counts over 100,000 per cu mm, *total body irradiation* is given according to the method described for chronic myelocytic leukemia. After remission is established, the blood picture is studied at intervals of one to two months and an x-ray treatment is given whenever the leukocyte count goes over 20,000 or 25,000 per cu mm. Our patients with lymphocytic leukemia have for the most part required less treatment to remain in remission than have the myelocytic group.

CASE IV—A woman, aged sixty-two years, was seen three and one-half years ago with a markedly enlarged spleen, a slight generalized adenopathy and a leukocyte count of 350,000, with 95 per cent mature lymphocytes. Following the initial treatments, she has received total irradiation on the average of every two to four months. The leukocyte count has varied from 15,000 to 35,000 and the spleen has remained palpable from 2 to 3 fingerbreadths below the costal margin. There is only slight adenopathy. The leukocyte count decreases after each x-ray treatment and then gradually rises before the next treatment is given. From the time that the disease was brought under control, she has remained entirely free of any symptoms. She has suffered no reactions from the x-ray therapy.

As with myelocytic leukemia, the lymphocytic type also reaches a stage when irradiation is no longer effective. At this stage there is fever, a progressive anemia and a fall in the platelets, usually to below 50,000 per cu mm. In the cases that have been seen in an advanced stage of chronic lymphocytic leukemia, lymphoblasts were not present in the peripheral blood.

One cannot always be certain that the patient has passed the stage when x-ray treatment will be effective, as evidenced by the following history:

**CASE V**—Recently, a male, aged sixty-six years, entered the hospital with a history of chronic lymphocytic leukemia of seven years' duration. He was thin and dyspneic. There was marked lymphadenopathy, the spleen extended to the pelvis, the liver was enlarged, and there was extensive edema of both legs. The blood picture was as follows: erythrocytes 1.4 million per cu mm., leukocytes 750,000 per cu mm., differential count 98 per cent mature lymphocytes and the platelets 48,000 per cu mm. After two red cell transfusions, a series of total body irradiation treatments was given. When next seen two months later the patient felt markedly improved and was able to work every day. The erythrocyte count was then 3.2 million per cu mm. and the leukocytes 20,000 per cu mm. The spleen and lymph glands had decreased in size and the edema had disappeared. When this patient was first seen, his chance of being benefited by x-ray treatment seemed remote.

Solution of potassium arsenite is relatively ineffective in the treatment of chronic lymphocytic leukemia.

In conclusion, it is apparent that much can be done to make the patient with leukemia feel better and to give him months or years of active living. Until a specific cure for leukemia is discovered, it is the physician's responsibility to use the available methods of treatment to the greatest advantage.

#### SUMMARY

For the purpose of treatment, leukemia is classified into the acute, subacute and chronic types. In acute fulminating leukemia, no treatment is of any avail. Blood transfusions cause considerable temporary benefit in the subacute types of leukemia. For the treatment of chronic leukemia, total body irradiation given at intervals to maintain continuous remission is

avored X-ray therapy\* used alternately with short courses of Fowler's solution (solution of potassium arsenite) also gives satisfactory results. With the proper use of irradiation, arsenic and blood transfusions the patient's general health and economic efficiency can be maintained for long periods.

\* The x-ray therapy in these patients was conducted by Dr. Earl E. Barth.

## HODGKIN'S DISEASE

RAPHAEL ISAACS M.A. M.D., F.A.C.P

HODGKIN's disease presents many problems both in diagnosis and treatment. With the cause unknown, many types of clinical manifestations and a difficult differential diagnosis, the condition warrants careful study. In the absence of a specific treatment, emphasis must be placed on what not to do.

### PRESENTATION OF CASES

The two cases presented here illustrate a benign and a malignant type, and emphasize certain features in diagnosis and treatment.

#### Case 1 Benign Type

*History*—The first patient, a young woman of twenty-six years, had considered herself well until about three years ago. At that time she noticed a "swelling" in the left pectoral region. The doctor watched it during the course of two months and as it did not respond to simple medication, it was removed. The mass proved to be an enlarged lymph node, and study of it led to a diagnosis of Hodgkin's disease. As frequently happens, as soon as the word "Hodgkin's" was mentioned the patient was rushed to a roentgen ray machine. Six treatments were given over the mediastinum, supraclavicular regions and left axilla.

One wonders why roentgen ray treatments were given. There is a mistaken impression that roentgen therapy is prophylactic, and that it will prevent growth of glands. In reality, in Hodgkin's disease, it reduces the number of lymphocytes, a process that is taking place as a part of the morbid condition.

At that time the blood was reported as "normal." In the early stages, when one lymph node is involved, there may be no gross change in the blood, quantitatively or qualitatively. Occasionally there is an increase in the number and percentage of lymphocytes, and plasma cells may be present in the blood stream. There is no basophilia of the granules of the neutrophils, as one would expect

in a pyogenic infection. As the disease progresses, other changes take place, and these will be discussed later.

Subjective symptoms developed slowly in this patient. She did not feel sick, but she tired easily. This is a common symptom, often one of the earliest in this disease as in many others. The exact mechanism of this symptom is not clear. It is not necessarily anemia, since it appears when the blood count is within normal limits. It appears when the urine is acid or alkaline, and is not correlated with any of the common blood chemical constituent variations. Occasionally there are symptoms of myocardial weakness, manifesting itself in shortness of breath on exertion. This however may be an evidence of generalized muscular weakness—an effect rather than a cause. There is a “sinking” feeling in the legs, amounting to actual pain at times.

This patient lost her appetite, ate less, and her weight decreased from 118 pounds to 105 pounds during the course of the first year. Her doctor prescribed “vitamins,” an arsenic preparation, and calcium salts. In spite of large quantities of mixtures of the various vitamin B components, as well as vitamins A and C, there was no therapeutic response. The arsenic was given because arsenic is given in Hodgkin’s disease. The calcium was for bleeding of the nose, a disability which she had noted since the age of fourteen or fifteen years. She noted but few of the common early symptoms of Hodgkin’s disease, such as pruritus, cough, fever, or pain.

A year after the appearance of the first symptom, enlarged lymph nodes developed on the left side of her neck and the left axilla. These receded after a second series of roentgen ray treatments. The unilateral appearance of enlarged lymph nodes, later bilateral, is characteristic of Hodgkin’s disease.

*Physical Examination*—The patient was first seen by us about four months after this episode. She was a slender, fairly well developed individual who tired easily. The cervical glands were not enlarged, but there were two small nodes palpable in the left, anterior triangle and one in the left axilla. They were discrete, hard, not tender and not adherent to the skin. The spleen was enlarged to 15 cm. on the left, and the liver to 16 cm. in the right mid-clavicular line. There was no gross abnormality of the heart, lungs, gastro-intestinal tract, or genito-urinary system.

*Blood Picture*—The blood at this time showed erythrocytes, 3,740,000 per cubic millimeter, leukocytes, 7300, hemoglobin, 10.4 gm per 100 cc, polymorphonuclear neutrophils, 80 per cent, lymphocytes, 5 per cent, monocytes, 5 per cent, eosinophils, 4 per cent, basophils, 1 per cent, cells noted in infectious mononucleosis, 2 per cent, endothelial cells, noted in conditions in which the liver is enlarged, 2 per cent, plasma cells, 1 per cent. The platelets were

increased in number Basophilia of the granules of the neutrophils was positive.

There was a moderate anemia, with "iron-deficiency" The polymorphonuclear neutrophils were increased in number and the lymphocytes definitely decreased This was about four months after the roentgen ray therapy, making it unlikely that the lymphopenia was one of the sequelae of this irradiation The presence of plasma cells indicated that pathological activity was going on in lymph nodes The infectious mononucleosis cells suggested possibilities for speculation Was the original disease an attack of infectious mononucleosis and were the subsequent developments pathological processes stirred up by the roentgen ray therapy? Against this was the pathologist's word that the gland removed was "Hodgkin's disease" Certainly the tissue showed the large Greenfield-Sternberg-Reed cells She may have had an attack of infectious mononucleosis at some time in her life, with the production of some of the abnormal cells for long periods thereafter (infectious mononucleosis cells have been recognized in a patient's blood seven years after an attack of the disease) Cells of this type were noted in this patient's blood during the next two months after which they were only rarely found

*Treatment and Course*—For treatment, several factors had to be considered There was the general nutrition, which was below par, there was a mild iron deficiency anemia, and the number of lymphocytes was low

For the improvement of the general nutrition an adequate diet was prescribed However financial considerations, rationing, as well as difficulty in preparing food in the room where the patient lived, made gain in weight a difficult problem Large quantities of "vitamins" of all kinds failed to influence either the appetite or weight

To improve the hemoglobin picture, we prescribed ferrous sulfate, 4 grains, three times a day There was no improvement during the course of three weeks A preparation of ferrous sulfate (10 grains per day) which contained some liver and "vitamins" was then substituted The hemoglobin increased from 10.4 gm per 100 cc to 12.6 gm in two weeks Thereafter the hemoglobin fluctuated from a low of 10.2 gm to 13.6 gm, depending on the profuseness of her menstruation

The erythrocyte count fluctuated from a low of 3,670,000 per cubic millimeter to 5,000,000

During the course of seventeen months the total leukocyte



count rose gradually from the lowest point of 6300 per cubic millimeter to 15,000

As Hodgkin's disease is "lymphotoxic," with a decrease in the number of lymphocytes in the blood stream as the disease progresses, an effort was made to increase the number of lymphocytes. Exposure to sunlight was always followed by the development of a rash, and had to be limited. The patient was then given an experimental extract of lymph glands, 1 gm daily. During the course of the seventeen months of observation, the number of lymphocytes increased from 584 per cubic millimeter to 1666 per cubic millimeter.

After seventeen months there are no changes in the two palpable lymph nodes, about 2 cm in diameter, in the anterior cervical triangle on the left side, and a similar node is palpable in the left axilla. The patient works regularly, and for all practical purposes appears in fairly good health. The progressive leukocytosis and the persistence of the palpable glands show that the underlying disease is still present. The peculiar papular rash developing on the extremities after exposure to sunlight has been diagnosed as "sun allergy." It must be remembered that skin lesions of many kinds appear during the course of Hodgkin's disease.

## Case II Malignant Type

Other features of Hodgkin's disease (rapid course, effect of too much roentgen ray therapy, and the development of features of a malignant neoplasm) are illustrated by the following case.

*History*—The patient is a man of forty-nine years, who considered himself in good health until about three months ago. He then noticed weakness, fever and developed pallor. The onset was rather rapid although the development of the symptoms covered three or four weeks. He went to a hospital where it was noted there was generalized enlargement of the lymph glands. One was removed, and the puzzled pathologist considered that it was a malignant tumor of some kind, possibly reticulum cell sarcoma or metastatic carcinoma. Roentgen ray therapy was started at once, with exposures over the anterior and posterior aspects of the mediastinum, the supraclavicular spaces, the inguinal regions, and both axillae. A total of 1850 roentgen units of irradiation was given in eleven days.

*Physical Examination*—The patient was first seen by us after the last treatment. He appeared pale and sick. He had a paroxysmal nonproductive cough. The peripheral lymph glands, including the epitrochlears, were enlarged. The tonsillar areas were depressed and the anterior pillars congested. There was an abnormal widening of the mediastinal dulness. In the first to the fourth interspaces, with the patient lying down, the dulness extended 5, 6.5, 6.5 and 5.5 cm. to the right of the midline, and 7, 11, 12, 13 and 11 cm. to the left. The pulse rate was 84 and blood pressure 100 systolic and 70 diastolic. The liver was enlarged to 16 cm. in the right mid-



Fig. 35—Enlarged hilar lymph glands (Case II)

clavicular line. The spleen measured 17 cm., but was not palpable. The dulness in the right hilar region posteriorly was enlarged to 16 by 8 cm. and on the left 16 by 10 cm. The enlarged hilar and mediastinal dulness indicated enlarged glandular masses, confirmed by roentgenographic examination (Fig. 35).

*Blood Picture*—The blood showed 4,000,000 erythrocytes per cubic millimeter, leukocytes, 11,000 per cubic millimeter, hemoglobin, 14 gm. per 100 cc. polymorphonuclear neutrophils, 74 per cent, lymphocytes, 4 per cent, monocytes, 22 per cent. Platelets were increased in number and vacuolated monocytes were present. The urine was not abnormal.

*Treatment and Course*—Although it had been the intention of the original operator to give more roentgen ray therapy, the patient was advised to discontinue it, as the lymphocytes numbered only 440 per cubic millimeter. It was felt that the findings on physical examination, as well as the blood picture (polymorphonuclear neutrophil leukocytosis, monocytosis, increased number of blood platelets, lymphopenia, increased by roentgen ray therapy) were compatible with the diagnosis of Hodgkin's disease.

During the next four weeks the leukocyte count decreased to 2000 per cubic millimeter and the number of lymphocytes fell to 240 per cubic millimeter. The erythrocyte count fell rapidly to 1,600,000 per cubic millimeter. A sternal puncture at this time showed practically complete aplasia of the erythrocyte-forming tissue and moderate hypoplasia of the leukocyte tissue. It was necessary to give ten blood transfusions in order to keep the erythrocyte count just over three million per cubic millimeter. On four consecutive days, 500 cc. of packed red blood corpuscles were given. This was equivalent to 4000 cc of whole blood. It caused an increase in the erythrocyte count from 2,000,000 to 3,470,000 per cubic millimeter.

A punctate rash appeared over the whole body, with edema of the face and legs. It was felt, at first, that this was a manifestation of Hodgkin's disease, but it was found that a previous doctor had prescribed phenobarbital, and that the patient had been taking this regularly for some weeks. The rash gradually faded and disappeared when the medicine was discontinued, and desquamation followed. The temperature ranged from 99.2 to 101°F, usually higher in the afternoon, but following no set pattern.

A lymph gland was removed and showed total loss of the normal architecture, with replacement by lymphoid cells, which invaded the capsule and surrounding tissues. There were many Greenfield-Sternberg-Reed multinucleated giant cells, with overlapping nuclei, and increased formation of connective tissue. This tissue had the characteristics of Hodgkin's sarcoma or reticulum cell sarcoma.

*Prognosis*—This type of Hodgkin's disease differs from that in the first case in that a lymphoid type of cell becomes "neoplastic," grows rapidly, and invades the surrounding tissues. There is generalized involvement of all the lymph tissue in the

body, including the mediastinal and abdominal glands. The vacuolated monocytes indicate that the gallbladder-bile duct apparatus is interfered with, and the enlarged regional nodes are causing obstructive pressure. Aplasia of the marrow has been caused by excessive roentgen irradiation. The prognosis now is extremely poor.

## DISCUSSION

### Terminology

Hodgkin's disease is known by many names in the literature: lymphogranuloma, pseudoleukemia, malignant granuloma, Sternberg's disease, Hodgkin's granuloma, Hodgkin's sarcoma, sarcomatous Hodgkin's disease. While many object to the use of an individual's name in designating a disease, everyone knows what is meant by Hodgkin's disease, whereas some of the other terms, having been used for other conditions, are confusing. Dorothy Reed<sup>1</sup> postulated: "We should limit the term Hodgkin's disease to designating a clinical and pathological entity, the main features of which are painless progressive glandular enlargement, usually starting in the cervical regions, without blood changes of leukemia. The growth presents a specific histological picture, not a simple hyperplasia, but changes suggesting a chronic inflammatory process. Eosinophiles are usually present in great numbers in such growths, but not invariably."

### Incidence

The disease involves individuals at all ages, but is two to three times more frequent in males than in females. There are less than 2000 deaths (average for the years 1934-1936 was 1614) per year known to have occurred from this disease in the United States. The rate is increasing slowly, being 0.6 per 100,000 for white men and 0.3 for white women in 1921 and 1.5 for white men and 1 for white women in 1937 in the standardized statistics of the Metropolitan Life Insurance Company. The percentage distribution of deaths for an average year (1936) was: Under fifteen years, 7.34 per cent; fifteen to forty-four years, 40.52 per cent; forty-five to sixty-four years, 34.87 per cent; sixty-five and over, 17.27 per cent.

At present, little can be said of the *etiology* of the disease. The problem is reviewed by Krumbhaar.<sup>2</sup>

## Diagnosis

Diagnosis is based on the clinical symptoms and course, on the blood changes, and on the study of sections of lymph glands

*Clinical Symptoms*—Symptomatology is the result of enlargement of the glands (pressure, pain, obstruction, dysphagia, engorged veins, pleural effusion, ascites, cough, diarrhea, constipation, jaundice, dyspnea, pulmonary symptoms, albuminuria, or edema), from associated toxemia (cachexia, loss of weight, fever, lesions of the skin, pruritus, headache, nausea, vomiting, weakness, mental depression, lymphopenia, chills, insomnia, anemia, leukocytosis, or elevated basal metabolic rate), or from metastatic growths or infiltrations (skin lesions, bone marrow invasion, bone lesions and neurological symptoms)

## SYMPTOMATOLOGY FROM ENLARGED LYMPH GLANDS IN HODGKIN'S DISEASE

### *Cervical, Submaxillary, Sublingual and Parotid Regions*

Pain in head and neck  
Difficulty in moving neck  
Dysphagia  
Pain in shoulders  
Dry mouth  
Pain in ear  
Pupillary changes  
Tachycardia  
"Bad taste in mouth"  
Headache

### *Axillary Glands*

Pain in shoulder and arm  
Edema of hand or arm  
Difficulty in moving arm  
Weakness of arm

### *Mediastinal and Hilar Glands*

Cough  
Dyspnea  
Dysphagia  
Tachycardia  
Nausea  
Pleural effusion

### *Inguinal Glands (Superficial and Deep)*

Pain in leg  
Edema of foot or leg  
Difficulty in walking  
Pain and edema of scrotum  
Weakness of legs

*Lumbar and Abdominal Glands*

Diarrhea  
 Constipation  
 Abdominal pain  
 Pruritus  
 Pain in back  
 Jaundice  
 Fever  
 Nausea  
 Anorexia  
 Ascites

*Spleen*

General weakness  
 Giddiness and dizziness  
 Headache  
 Constipation or diarrhea  
 Pain in left upper quadrant of the abdomen  
 Vomiting  
 Nausea  
 Cough  
 Palpitation  
 Feeling of fullness or dragging in left upper quadrant of the abdomen  
 Abdominal discomfort  
 Midpigastrie pain  
 Anorexia  
 Fever  
 Jaundice  
 Pain on deep inspiration  
 Pain in left side of chest  
 Pain in left shoulder  
 Tenderness over the spleen region  
 Pain in the "back"  
 Pain in the left leg  
 Discomfort in certain positions  
 Night sweats  
 Hemorrhoids  
 "Buzzing" in the ears  
 Gastro-intestinal upsets  
 Difficulty in bending  
 Tenderness of trapezius or left deltoid muscles  
 Dysphagia  
 Soreness of the inner surface of the left thigh  
 "Tightness" of the left knee  
 Swollen left testicle  
 Friction rub in left axilla  
 Pain in left arm  
 Visual disturbances  
 Left pupil smaller than the right  
 Elevation of cardiac apex (pseudo left axis deviation in electrocardiogram)  
 Congestion of abdominal blood vessels  
 "Heartburn"

A characteristic type of fever (Murchison, Pel-Ebstein) has been described. This is marked by a gradually increasing fever which reaches a maximum and then declines to a normal level. The febrile period and nonfebrile periods may last from two weeks to months. However, in actual practice, perfect examples of this type of fever are seldom seen. No doubt the use of aspirin, roentgen ray therapy and antifebrile measures disturb the picture. Great debility and enervating perspiration may accompany these periods.

In many individuals symptoms of an elevated basal metabolic rate may appear, with perspiration, rapid pulse rate, tremors, loss of weight, irritability and nervousness.

*Blood Changes*—The blood changes in Hodgkin's disease vary with the type and the stage of the disease. In the advanced stages there is a progressive anemia, either from hypoplasia of the marrow or from development of the Hodgkin's growth in the marrow cavity. The anemia is usually of the hypochromic type, with some cases showing considerable variation in the size and shape of the erythrocytes, occasionally stippled cells, rarely normoblasts. In the type with the aplastic bone marrow, the erythrocytes may be uniformly round and show but little variation in size. The erythrocyte count may, however, remain within normal limits for years. As the disease progresses, the erythrocytes, in films, may show marked rouleau formation and autoagglutination, reflected in a rapid sedimentation rate.

The platelets are usually increased in number, and the bone marrow shows an increase in the number of megakaryocytes.

There are two types of the disease as evidenced from the leukocyte count. In one type, the "uncomplicated" Hodgkin's disease, there is a tendency for the leukocyte count to increase, commonly to 15,000 to 18,000, occasionally to 50,000 or over 100,000 per cubic millimeter. As a rule the leukocytosis is neutrophilic in type, occasionally eosinophilic. The eosinophils, commonly increased in number in the lymph glands and tissues, may or may not be increased in number in the blood. The Gordon test runs parallel to the number of eosinophils, and is not a specific test for Hodgkin's disease. With the progress of the disease the lymphocytes decrease in number to extremely low levels. The monocytes may be more numerous than normal. The first case described here illustrates this type.

In the second type, corresponding to the sarcomatous Hodg-

kin's group, including the variety called Hodgkin's sarcoma, the leukocyte number is not increased, or is quite low. The number may be from 1000 or 2000 to 6000 per cubic millimeter when the disease begins to become well developed. In this type the absolute lymphocyte number may be decreased, although relatively the percentage may not be as low as in the other type of Hodgkin's disease. The second case described here is of this type.

Occasionally small forms of the Greenfield-Sternberg-Reed cells are found in the blood film. They may be mistaken for atypical monocytes. Plasma cells are noted frequently. Bone marrow puncture is helpful in ruling out other lesions, although rarely the needle may enter a region of Hodgkin's tissue, and is then of direct diagnostic value.

The two types of blood picture, as well as the secondary changes which follow roentgen ray therapy, have led to the general statement that there is no characteristic blood picture in Hodgkin's disease.

### Prognosis

The prognosis varies with the rapidity of the disease process and the caution used in treatment. There are rapidly growing and slowly growing forms of the disease, and a rare acute form is encountered. Some patients survive twenty-six years or more, whereas others live but a few months. The variations are so great that the term "average duration" has but little significance at present. Certain features suggest a bad prognosis: high or progressive fever, short duration of remissions after roentgen therapy, progressive and marked anemia, gross involvement of the abdominal lymph glands, generalized involvement of all the glandular areas, coincident disease of other types, as tuberculosis, progressive cachexia, excessive and unwise roentgen therapy.

### Treatment

For treatment, the use of roentgen rays, radium or radioactive substances appears to be most effective in relieving symptoms. Irradiation is not prophylactic or curative. It is wise to limit the treatment to the lowest possible exposure and to avoid it when the lymphocyte count is low. The virtual wiping out of the lymphocytes in the second patient described here, and the production of erythrocyte aplasia of the marrow are examples



of treating the lymphoid tumors and forgetting the patient. Much improvement may follow proper roentgen ray treatment of the bone lesions which may be present in the disease.

Long remissions have followed removal of isolated, diseased nodes. We have seen a flare-up of the disease in cases of removal of part of the nodes, with others remaining in the region. The biopsy wound, however, is not involved in the process, as may follow in tuberculosis or lymphosarcoma. Blood transfusion, when needed, is a valuable temporary measure. Arsenic in the form of Fowler's solution appears to have a beneficial effect on the disease as a whole in a few patients, but does not help others. It may accentuate the normal tendency to pigmentation in this disease.

Any therapy which would tend to increase the number of lymphocytes would be of value. Sunlight and ultraviolet irradiation appear to have some value, although it is limited. Certain experimental extracts of lymph glands appear to have value in cases which have not advanced too far. For the fever, aspirin and tepid sponges give subjective relief.

Cough may be a severe and difficult symptom. Frequently it is the result of enlarged mediastinal or hilar lymph nodes (Fig 35). Codeine and the commonly employed cough medicines are usually ineffective. Some relief may follow roentgen ray therapy over the mediastinum or the hilar nodes. When the nodes become sclerotic, little help can be expected from roentgen ray therapy.

Herpes is a troublesome complication. Locally "carbulated vaseline" or similar preparations may give temporary relief from pain. Roentgen ray therapy over the vertebral region may be tried. Some patients are helped by the intravenous administration of sodium iodide, 15 grains in 10 or 20 cc of water on two or three consecutive days.

Pruritus may respond to roentgen ray therapy over the vertebral region, especially in the lumbar part. Local and internal medication is seldom helpful. The usual antipruritic substances, especially phenol, may give temporary relief. Tincture of belladonna, 10 minims, three times a day before meals may be tried. Among the supportive measures advocated are the administration of iron, viosterol, vitamins and iodides. The results vary considerably from patient to patient.

The prognosis in Hodgkin's disease is not necessarily as

gloomy as the earlier accounts indicated Treatment must be given extremely carefully, as more damage may be done by over-treatment or unwise treatment than would be done if no treatment at all had been given Much good may be accomplished by proper therapy

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# PERNICIOUS ANEMIA\*

STEVEN O. SCHWARTZ, M.D.

## DEFINITION

PERNICIOUS anemia is a disease usually insidious in onset and protracted in course, manifesting itself as an involvement of the hemopoietic, gastro-intestinal and nervous systems with differing degrees of intensity. Involvement of the hemopoietic system results in a megaloblastic bone marrow and varying degrees of anemia, leukopenia, granulopenia and thrombocytopenia. Prime manifestation of gastro-intestinal involvement is the atrophy of the gastric mucosa with an accompanying achlorhydria and achylia, while degenerative changes of the posterior and lateral columns of the spinal cord characterize the nervous system changes. The administration of liver induces a remission in the manifestations of the disease.

## HISTORY

Thomas Addison is credited with the original description of pernicious anemia, though his concept of the interrelationship with suprarenal gland disease was incorrect, and several writers recorded the disease before him. His masterly description published in 1855<sup>1</sup> has well earned him the eponym, albeit in strict justice credit for priority should go elsewhere. Combe<sup>16</sup> in 1822 is said to have been the first to report an authentic case, while others were published by Andral (1823), Hall (1837), Piörty (1841), Pearce (1845),<sup>31</sup> Elliotson (1846),<sup>19</sup> and Barclay (1851).<sup>6</sup> Channing as early as 1842,<sup>13</sup> recognized a severe pernicious anemia-like picture in the puerperium and discussed the use of blood transfusions in its treatment. Biermer,<sup>8</sup> unaware of Addison's work, reported fifteen cases in 1871 and is often credited by German writers with priority, even though another German, Lebert, had published two cases previously.

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\* From the Hematological Laboratory, Cook County Hospital. Aided by a grant from the Wilson Laboratories.

By 1860 when Wilks pointed out the absence of an increase in the white blood cells, much interest was manifested in both the clinical and pathological aspects of the disease. Greatest progress, in retrospect, was made between 1874 and 1888. In 1874 Immerman called attention to the fever which accompanied the disease (an association also noted by Biermer) and attributed it to the anemia. In 1875 Pepper and a year later Cohnheim<sup>15</sup> described accurately for the first time the changes in the marrow and suggested that these were responsible for the anemia. During the same year Quinke<sup>45</sup> depicted the rich iron deposits in the liver, pancreas, kidneys and other organs and pointed out the difference in the size of the red blood cells, calling attention to their variations in shape, which he named poikilocytosis. The next year Bromwell was reporting favorable results in some cases following the administration of arsenic, and three years later Fenwick<sup>21</sup> not only recorded that the gastric mucosa was atrophic but clairvoyantly expressed the view that the symptoms of the disease were the results of this rather than the secondary deficiency of the blood. Between 1880 and 1883 came Ehrlich's discovery of nucleated red cells in the circulating blood, Eichhorst's finding of the microcytes, and Laache's observation on the disproportionately high hemoglobin-red cell ratio and emphasis of the large, deeply colored red cell which he thought characteristic. Soon afterwards Lichtheim (1887) recognized the pathological, and resultant clinical, nervous system changes.

Momentum was given the theory of parasitic etiology by the findings of *Ankylostoma duodenale* by Baumler (1881) and Sahli (1883) and *Dibothriocephalus latus* by Rehber (1884) and Runcberg (1888) in cases of apparent pernicious anemia. But Hunter, basing his thesis on the increased stores of iron, the hyperplasia of the bone marrow, and evidences of blood destruction, postulated a toxic, hemolytic causation.

There is little of significance, excepting the increasingly widespread use of blood transfusions and the brief era of splenectomy, separating these early years from the "modern" era. Basing his observations on the efficacy of liver in relieving dogs made anemic by bleeding, Whipple<sup>60</sup> suggested that there might be a scarcity of red cell stroma building material in pernicious anemia. Minot, prompted by this work and the knowledge that liver was of benefit in sprue, together with Murphy<sup>42</sup> began

feeding large amounts of liver to patients and by 1926 had become satisfied with both the objective and subjective response to this therapy. Soon Cohn and Minot<sup>14</sup> were able to show that oral extracts of liver were as efficacious as the whole organ, and not long afterwards Ganssle prepared the first practical parenteral extract.

The next milestone is represented by Castle's experiments<sup>11, 12</sup> showing that pernicious anemia is the result of a lack of the so-called "intrinsic factor," which is normally produced by the stomach and interacts with certain foods containing the "extrinsic factor" to produce the "anti-pernicious anemia principle." Sturgis and Isaacs<sup>61</sup> (1929) showed that stomach tissue had properties similar to liver, and since then these properties have been demonstrated in kidney, brain, placenta and other organs. Much has been written and many of the finer clinical and hematological details clarified in the intervening years, but with the exception of the concentration of the liver extract and attempts at the establishment of its chemical identity, with the view of synthesis, no further progress has been made.

### ETIOLOGY

Pernicious anemia results from the failure of the gastric mucosa to elaborate the "intrinsic factor" of Castle, which is normally produced in the pyloric portion of the stomach in man.<sup>30</sup> When the "intrinsic factor" is absent or markedly diminished,<sup>26, 29</sup> no "anti-pernicious anemia principle" is formed by interaction with the "extrinsic factor."<sup>59</sup>

The "anti-pernicious anemia principle" is stored in the liver<sup>51</sup> and thence supplies the functional needs of the bone marrow, the integument and its appendages, and the central nervous system. Occasionally destruction of the "intrinsic factor" producing portion of the stomach by disease,<sup>25</sup> chemicals,<sup>2</sup> or surgery<sup>40</sup> will give rise to pernicious anemia. Infrequently, diets abnormally low in "extrinsic factor" may have the same results.<sup>8, 27</sup> Pregnancy, *Ankylostoma duodenale*, *Dibothriocephalus latus* and many other infestations and conditions have been incriminated as etiologic agents, but considerable doubt exists whether these are truly etiologic agents or merely precipitating factors in latent cases.

## INCIDENCE

Although pernicious anemia occurs most frequently in Caucasians from the temperate regions,<sup>23 24</sup> exceptions are so numerous that one cannot rely on nationality as a diagnostic aid. It is said to be unusual in the Negro, but we have recently shown<sup>54</sup> that its incidence has been much underestimated. The same is probably true for its rarity in Orientals, I myself having observed the disease in three Chinese. Seventy-five per cent of the cases occur between the forty-fifth and seventy-fifth years, but the age range is extreme. The occurrence in young children is debatable, though an occasional case is reported. Our youngest proved case was in a girl of seventeen.<sup>55</sup> We have noted a progressive increase in the rate per 100,000 beginning with 0.5 in the decade between ages ten and nineteen and reaching 553 in the decade between ages seventy and seventy-nine. There is a falling off of the rate above this but this falling off is probably more apparent than real (Tabulation)

## TABULATION

## INCIDENCE OF PERNICIOUS ANEMIA ACCORDING TO AGE

Age Group	Rate per 100 000
10-19	0.5
20-29	4.5
30-39	21.0
40-49	66.0
50-59	157.0
60-69	310.0
70-79	553.0
80-89	191.0

In our experience males and females have been about equally affected (495 males and 505 females)

Heredity is not of great significance, yet there is a distinct familial incidence, about 18 per cent of the patients<sup>21</sup> having relatives with the disease. Five proven cases in one generation,<sup>56</sup> occurrence in twins and in successive generations<sup>5 57</sup> have all been reported, and I am aware of a family where three successive generations of daughters are affected. The finding of hypochromic anemia and achlorhydria in the families of patients with pernicious anemia is too frequent to be dismissed as pure coincidence.

Draper<sup>18</sup> has described the pernicious anemia "type" as a

person having medium to tall build, broad face, large mandibular angle, short nose, long thin ears, wide, deep and short chest, wide subcostal angle, highly placed umbilicus, long abdomen, relatively wide pelvis and long lower extremities, eunuchoidal habitus, and feminine quality of the secondary sex characteristics in the male To this description we may add the broad spadelike hand and the usually massive bony structure, as well as the light eyes and light hair, which turns gray at an early age<sup>24</sup>

### SYMPTOMS

The symptoms of pernicious anemia usually appear so slowly that the patient cannot date the onset of the illness or its first manifestation with any exactitude For the most part the symptoms may be divided into four groups (1) general complaints, (2) those referable to the cardiovascular system, (3) those to the gastro-intestinal tract, and (4) to the nervous system This arbitrary division, though highly artificial since close interrelation and interdependence exists among the expressions of the disease, is justified by convenience for descriptive purposes

#### General Complaints

Most frequent complaints are *weakness* and a *sense of being unwell*—one or both of these being present in almost every case The degree of weakness is variable and may be so mild as to manifest itself only as slight lassitude or may be severe enough to cause total disability When extreme, the slightest exertion becomes impossible—the profound “languor” of which Addison spoke almost a hundred years ago With the weakness go also the symptoms due to the anoxia of the central nervous system such as faintness, dizziness, inability to concentrate, loss of memory, ringing in the ears, spots before the eyes, occasional blurring of vision and a sense of coldness As a rule the development of the general symptoms parallels the fall in the hemoglobin level

#### Cardiovascular Symptoms

The symptoms referable to the cardiovascular system follow even more closely the level of the blood Few cardiovascular manifestations are noted while the hemoglobin is above 50 per cent (8 gm), and in the slowly developing cases the paucity of complaints even with the hemoglobin level at 20 per cent (3 to

4 gm ) or less is astonishing. It is to be remembered in this connection that it is the hemoglobin and not the red cell level that is of importance here since the individual cells contain more than their normal complement of hemoglobin and this determines the oxygen carrying capacity of the blood.

*Dyspnea*, appearing at first only after exertion and later with increasing ease, occurs in the majority of patients by the time they present themselves for examination.

*Edema* is the second most important symptom and depends for its development on cardiac dilatation and subsequent relative failure, on tissue anoxia, on lowered blood proteins, and the anemia itself. It is usually confined to the legs but may be more extensive.

*Palpitation* is almost as frequent a complaint as dyspnea, and is at first also noted particularly after exertion, though occasionally there is a constant awareness of the heart "pounding" even when lying down. With severe anemia, especially in the presence of changes in the coronary vessels, such as arteriosclerosis, where the blood supply of the heart muscle is already impaired, angina pectoris may be a complication.<sup>63</sup> With the amelioration of the anemia the pain disappears in most instances.

#### Gastro intestinal Symptoms

Most prominent among the gastro-intestinal symptoms is the *loss of appetite*. This may vary from a mild distaste for certain foods to anorexia so marked that little besides milk and cereals are eaten. To aggravate matters, the most essential food substances are the first ones eliminated. Dairy products, cereals and starches constitute the diet in the average case. Aversion to meat is so common as to bear special mention, the usual reason given being the "inability to digest it" and the "loss of taste for it." Frequently much patience and persuasion are required to re-educate the patient to eat a balanced diet, and meat in particular, even after the therapeutically induced remission.

*Epigastric distress*—usually described as "pains in the stomach"—and nausea and vomiting are the symptoms next in importance. Diarrhea is one of the "text-book" symptoms, but in our experience occurs in no more than a tenth of the cases, while alternating diarrhea and constipation is seen only in about 5 per cent. We have, on the contrary, found *constipation* to be the rule, occurring in well over half the cases.



The intensity of gastro-intestinal complaints roughly parallels the tongue changes, since in general the more extensive the atrophy of the tongue the more marked the atrophy of the upper gastro-intestinal mucosa<sup>33, 38, 52</sup> The *tongue symptoms* in turn follow the atrophic changes seen in the papillae Varying degrees of tongue changes occur in almost all cases but tongue symptoms will be volunteered by only about a fourth of the patients They are variously described as "burning," "smarting," the sensation of "acid" on the tongue, or as intolerance to sour, salty, hot and occasionally rough foods Sometimes these sensations extend to the oral mucous membranes and the gums, leading to the mistaken diagnosis of "oral sepsis" with subsequent extraction of the teeth Many patients date their symptoms to the time the teeth were pulled, little realizing the cause-and-effect relationship

The emphasis on the preservation of the body tissues, persisting since Addison's time, has made us lose sight of the fact that great changes in weight occur We have found *weight loss* in almost every case during relapse and it was one of the presenting complaints in fully 60 per cent Even more striking than the history of weight loss is the remarkable gain in weight after therapy is begun This gain in the average case amounts to from 10 to 25 per cent of the body weight<sup>34, 64</sup>

### Symptoms Referable to the Nervous System

Symptoms referable to the nervous system occur in four out of five cases Earliest and most common complaints are "*tingling*" and/or "*numbness*" of the finger tips, present bilaterally and usually symmetrically The characteristic way in which patients describe this is by gently rubbing the thumb over the other fingers in rotation to indicate the site of involvement The lower extremity is usually affected subsequently At first the toes become numb, then there is a gradual extension upward with an increasing feeling of *coldness* Still later the leg becomes unsteady and there are peculiar subjective sensations variously described as walking "on air," "on clouds," "on pillows," "on rubber," and so on In later stages there may be an awareness of staggering and the feeling of "walking as if drunk"

The coldness and numbness may in time involve all the extremities and the entire trunk, though the upper arms and thorax are usually spared Walking, due to the loss of position sense

and the spasticity of the lower extremities, by this time has become impossible. Responsible for the symptoms are the degeneration of the posterior columns of the spinal cord carrying primarily proprioceptive and joint position sensations. When degenerative changes in the posterior columns dominate, spasticity is not a remarkable feature, on the other hand, when the dominant degeneration is in the lateral columns, spasticity is foremost. Stiffness and/or numbness leading to *difficulties in walking* are among the outstanding symptoms, being present in a mild form in about half and in a severe form in about a quarter of the cases. *Genito-urinary involvement*, manifesting itself particularly in bladder incontinence and decreased sexual desire in the male, is not uncommon. *Rectal incontinence*, frequently accompanying that of the bladder together with trophic changes, predispose to complications which unfavorably affect prognosis.

#### SIGNS

The common, though by no means constant, anthropological features found in patients with pernicious anemia have already been mentioned. There are a few other signs which are the rule but here again exceptions are numerous. *Pallor*, especially of the mucous membranes, is most frequent and varies with the degree of anemia. *Jaundice*, varying from a faint trace, visible only in the sclerae (icterus index 8 or 10), to frank jaundice (icterus index 25 or 30) appears in inverse proportion to the anemia. It imparts a yellowish cast to the skin, so often and so incorrectly referred to as "lemon-yellow" pallor. Rarely jaundice may be even more marked, but this most frequently occurs in complicated cases, cases with gallbladder or liver disease.<sup>7</sup>

The importance of the tongue as a diagnostic aid cannot be overemphasized, notwithstanding the fact that deviations from the typical *smooth tongue* are many. The completely bald, shiny, glistening tongue with all its papillae completely atrophied occurs in no more than 15 to 20 per cent of the cases—and when it does occur, unless complicated by dietary deficiencies, it is not "beefy red" but rather a pale, bloodless, orange-red ("veal-like"). The absence of a "coat" from the tongue has been the least variable and the most important sign. A coated tongue is sometimes seen but these exceptions are so infrequent as to lead to little confusion, and help but to emphasize the fact that pernicious anemia is indeed *a disease of exceptions*.

Changes in the heart are those secondary to the anemia, and as such vary with its severity. Dilatation is the rule and is best observed in the roentgenographic silhouette, which shows progressive shrinkage with improvement in the blood. Soft *hemic murmurs* appear when the hemoglobin falls below 50 per cent. They are usually systolic in time and are confined to the apical and pulmonary areas at first, but with the progression of the anemia may be heard over the entire precordium and in diastole as well. The presence of murmurs may lead to a mistaken diagnosis of heart disease, as we have had occasion to point out elsewhere.<sup>53</sup> A lowering of the blood pressure, usually not marked, is the rule, and is more pronounced in the systolic reading than in the diastolic. The electrocardiographic changes are non-specific and manifest themselves most commonly as low voltage, low or inverted T's, and lowered S-T segments.

Demonstrable *enlargement of the liver* is present in a fourth of the cases and it is not unusual to palpate the lower border 6 to 8 cm below the costal margin. The liver edge in these cases is firm, sharply demarcated, and nontender. *Splenomegaly* of sufficient magnitude to make the spleen palpable is only found in from 10 to 20 per cent of the cases. This may be quite marked at times, the lower border reaching 8 or even 10 cm below the costal margin. Shrinkage of both the liver and spleen follow induced remission. The persistence of splenomegaly in a treated case indicates a complication,<sup>9</sup> but it is not unusual to find some residual liver enlargement.

Some *edema of the legs* is seen in almost every case with a hemoglobin level below 50 per cent (7.5 to 8 gm). It becomes marked in only 10 to 15 per cent of cases, and may be very extensive at times, manifesting itself on rare occasions as generalized anasarca. When this occurs, the prognosis becomes extremely grave.

Neurological signs most commonly encountered are the *loss of vibration sensation* in the lower extremities, *changes in deep reflexes*, the appearance of pathological reflexes, *loss of position sense*, and the appearance of a positive *Romberg sign*.<sup>58</sup> The earliest change is a quantitative diminution in vibration sensation at the level of the ankle. Gradually this spreads upwards and may reach the thoracic level with complete loss of vibration sense below. The deep reflexes (knee and ankle jerks) will be either hyperactive or hypoactive depending on whether the

posterior or lateral columns dominate. More extensive involvement of the posterior columns will lead to hypoactive deep reflexes while more severe lateral column damage will lead to hyperactivity. The former occurs twice as frequently as the latter. The appearance of pathological reflexes also depends on disproportionate lateral column degeneration.

*Gait difficulties* are essentially of two kinds: those depending on the loss of position sensation and hypotonicity and manifesting themselves as inability to walk in the dark, and as having a positive Romberg sign, and those due to spasticity and manifesting themselves in the typical scissors gait. Far more common than pure examples of either are combinations with one or the other type dominating.

Occasionally involvement of the cranial nerves is encountered the *loss of the sense of taste and smell* being the most common. Visual difficulties occur at times but are more usually due to hemorrhages in the fundi than to optic nerve changes.<sup>37</sup>

A dulling of the sensoria secondary to the anemia of the brain is extremely common, and its significance lies in the fact that the anoxic changes may at times be irreversible. *Psychotic manifestations*<sup>30</sup> may even lead to the mistaken diagnosis of psychiatric disease. Because these patients usually have in addition the complicating urinary and fecal incontinence, the trophic skin changes, and decubitus ulcers, their prognosis is as a rule very poor.

#### LABORATORY FINDINGS

Most pertinent of laboratory findings in pernicious anemia are those in the blood. The degree of *anemia* is extremely variable. In cases showing neurological changes primarily the anemia may be so insignificant as to cause diagnostic difficulties,<sup>49-52</sup> or the count may go to incredibly low levels, the writer having seen the red cell count as low as 340,000. Characteristically the blood shows an *anemia, leukopenia, granulopenia* and *thrombocytopenia*.

The changes in the red cells may be considered pathognomonic and are characterized by *macrocytosis*, the large cells being ovoid in shape and, because of increased thickness, seem more highly colored than normal, with the resultant appearance of "*hyperchromia*." Microcytosis is the earliest change and may be found even with red cell levels at four million. As the ane-

mia progresses the macrocytosis becomes more pronounced and at about a two and half million level *anisocytosis* and *poikilocytosis* appear. With progression of anemia these changes become more and more extreme. Rarely, when iron deficiency complicates the picture, the macrocytosis may be absent but the other changes are nevertheless present.

The presence of a leukocytosis before therapy is usually indicative of complications. Accounting for the leukopenia is not only the depression in granulocytes but also in lymphocytes. There is a right shift of the neutrophils with mature forms dominating, and many of the cells showing multiple lobulations of their nuclei.<sup>35</sup> The white cell count averages between 5000 and 6000 but drops sometimes to 1000 or 2000. Platelets are diminished in almost all cases,<sup>44</sup> but the diminution is rarely of such magnitude as to lead to clinical symptoms.

The second most informative laboratory test is the analysis of the gastric contents which, with extremely rare exceptions,<sup>22, 48</sup> shows an *achlorhydria* and *achylia*. The exceptions to this rule are so few as to make one discredit the diagnosis of pernicious anemia without very substantial additional proof. The *icterus index* is elevated<sup>41</sup> from 10 to 20 and on rare occasions may even rise over 30 in uncomplicated cases. Urobilinogen in the urine is also increased.<sup>20</sup>

The determination of the *reticulocyte count* for practical purposes is unimportant, but is of aid in determining the potency of liver extract, and may be of value when liver is employed in a therapeutic test. In untreated cases the reticulocytes vary between 0 and 5 per cent, and start to rise about two days after the beginning of therapy. The reticulocytes reach a peak, whose magnitude is inversely proportional to the level of the original count,<sup>32</sup> in five to seven days, on intramuscular liver therapy (40 per cent starting at one million, 20 per cent at two million, 10 per cent at three million). *Red cell increase* begins simultaneously with reticulocyte response and also rises at a rate inversely proportional to the original erythrocyte level.<sup>46</sup> The simplest way of calculating the expected daily rise is to divide the difference between the original and ideal red cell levels by 60 since regardless of the original blood level the normal count will be reached in about eight weeks.

The finding *sine qua non* is the *megaloblastosis* of the bone marrow.<sup>17</sup> This must be present in every case in which the his-

tory, physical finding, neurological changes without anemia, or the presence of free hydrochloric acid makes the diagnosis questionable

### CONCOMITANT DISEASES

Although individuals who have pernicious anemia may develop the same complicating diseases as others in similar age groups, there are certain illnesses that apparently occur with increased, while others with decreased, frequency. *Peptic ulcer* is said not to occur,<sup>26</sup> and explanation for this may be found in the achlorhydria and the emotional makeup. *Tuberculosis* is also said to be rare,<sup>25</sup> though roentgenographic evidence of primary infection is seen frequently. We have seen active tuberculosis in patients with pernicious anemia, though, considering the increased susceptibility, the incidence should be greater. Prominent among other complicating conditions are *arthritis*, *diabetes mellitus*<sup>26</sup> and *asthma*.

*Thyrotoxicosis*, in our experience, has shown an unexpectedly high incidence, considering the fact that it is supposed to occur in an entirely different age group and in individuals of different constitutional predispositions.<sup>4, 41</sup> Thyrotoxicosis may precede or develop during the course of pernicious anemia. When the anemia develops after thyroidectomy in these cases it is not the macrocytic anemia occasionally encountered in the course of myxedema, but fulfills the strict diagnostic criteria of pernicious anemia, is accompanied by an elevated basal metabolism, and responds specifically to the administration of liver extract without additional thyroid.

*Gallbladder disease* also shows a significantly increased<sup>70</sup> incidence,<sup>7</sup> which may be secondary to the increased pigment metabolism.

The termination of pernicious anemia in *carcinoma of the stomach* has been emphasized in the literature, metaplasia of the atrophic gastric mucosa with polyp formation and carcinomatous degeneration being postulated as the cause.<sup>23, 62</sup> Considering the commonness of carcinoma of the stomach and the overlapping of the age groups in which both conditions are found, one may well question the validity of the emphasis placed on the relationship of the two diseases. In a large series of cases followed over a long period of time, I have been unimpressed by the frequency of stomach carcinoma.

## DIAGNOSIS

The diagnosis of pernicious anemia is very easy when there are changes in the blood, the nervous system and the gastro-intestinal tract. Diagnostic difficulties are most likely to be encountered when a single symptom is disproportionately prominent and the others are either absent or insignificant. Thus a patient having only anemia might be suspected of *cardiovascular disease* because of the symptoms—a suspicion confirmed by the hemic murmurs, the occasional splenomegaly, and the fever.<sup>58</sup> Patients complaining of anorexia, nausea, vomiting and epigastric pains may be assumed to have *gastro-intestinal disease* especially when weight loss and change in bowel habits are added to the symptoms. *Primary neurological disease* is often diagnosed when the anemia is mild or absent, a circumstance by no means uncommon since there is usually a reciprocal relation between the severity of the anemia and the nervous system involvement.<sup>60, 62, 67</sup>

At first glance the appearance of the patient may suggest *nephritis* or *myxedema*, but these diseases can be easily differentiated clinically. Hematologically, sprue,<sup>10</sup> fish-tapeworm infestation and carcinoma of the stomach are said to lead to confusion most frequently, but in our experience *aleukemic leukemia*, *myelophthisic anemia*, and *aplastic anemia* have caused the greatest diagnostic difficulties.

The rules to follow in attempting to diagnose pernicious anemia are

- 1 Suspect pernicious anemia in every case where no *obvious* cause for the anemia exists, where vague abdominal discomfort is associated with anemia, or where paresthesias of the extremities coexist with anemia or gastro-intestinal symptoms. At this stage pernicious anemia is suspected.

- 2 Examine the patient, looking in particular for the anthropological features described above, the gray hair, light eyes, pallor, scleral icterus, atrophy of the tongue papillae, the presence or absence of lymphadenopathy, hepatomegaly and splenomegaly. Neurologically, changes in the deep reflexes, a positive Romberg sign and loss of vibration sensation are looked for. Should confirmatory information be supplied by the examination, a tentative diagnosis of pernicious anemia may be made.

- 3 If the blood presents anemia with a high color index, leukopenia, thrombocytopenia and granulopenia, if the red cells

are large and oval, and are well filled with hemoglobin, and in addition show alteration in size and shape (not at high red cell level<sup>1</sup>), and if in addition multilobed polymorphonuclear leukocytes are seen, the probable diagnosis of pernicious anemia may be made, and liver therapy begun lest the patient be jeopardized by waiting.

4 While awaiting therapeutic response (five to eight days) the following confirmatory tests should be performed

- (a) Icterus index or Van den Bergh determination
- (b) Urinary urobilinogen determinations  
(These must be performed within twenty-four to forty-eight hours since their values drop markedly thereafter)
- (c) Analysis of the gastric contents following histamine stimulation (twenty to thirty minutes after the administration of 0.1 mg of histamine hydrochloride per 10 kg body weight subcutaneously)
- (d) Stool examination for occult blood and parasites or their ova

If the bilirubin of the blood and urobilinogen of the urine are increased, no free acid is found in the gastric secretions, and neither blood nor parasites are present in the stool, a positive diagnosis of pernicious anemia may be made.

Occasionally one may wish to hasten making a positive diagnosis or may wish to confirm it with examination of the marrow whose changes are pathognomonic.<sup>17</sup> But even in cases thus diagnosed, the above described tests should be performed to rule out a pernicious anemia secondary to gastric neoplasm, fish tapeworm, or other causes.

#### TREATMENT

*Liver extract* is specific for the treatment of pernicious anemia. Only general rules can be formulated as to the mode of its administration, since individualization of the patient<sup>18</sup> is as important, or is even more important, than in other diseases where specific therapeutic agents are known. One unit\* of liver extract per day on the average is required for maintenance, but extreme variations are encountered.

Cases may roughly be divided into two groups, depending on the presence or absence of neurological signs and symptoms.

\* A unit is defined as the amount of liver which when given in a uniform daily dose in a case of pernicious anemia in relapse will elicit a satisfactory red cell and reticulocyte response.



*Patients without neurological complications* should get an average of 15 units of liver extract intramuscularly three times a week for the first two weeks, twice a week for the next two weeks, and weekly for the next month. By the end of this time (eight weeks) the blood has reached a normal level. From here on doses of 15 to 30 units of liver extract can be given anywhere from once a week to once every four to six weeks depending on individual requirement. The best plan is to "wean" the patient by cutting the frequency of injections by a week every two to three months. There is little merit in examining the blood at intervals less than two to three months, since the patient's sense of well being, the paucity of complaints, the color, and the appearance of the tongue are sufficiently good indices of adequate therapy. Once the maintenance dose is established there need be little deviation from it unless complications (infections, bleeding, pregnancy, and so forth) occur. The need for liver increases considerably when complications are present and allowance must be made for this by increasing either the dose or the frequency of administration, or both. The site of injection depends on preference. We have found the upper portion of the deltoid muscle the site of choice, here amounts up to 3 cc are tolerated without discomfort.

Treatment in *cases complicated by neurological symptoms* is much more intensive. In general, 20 to 30 units are given daily for the first two weeks, three times a week for four to six weeks, then twice weekly for another four to six weeks, and finally weekly until all neurological symptoms shall have disappeared, or until no further improvement is thought possible. Such intensive treatment should be continued for at least two years before one may assume that no further improvement is possible. Improvement in neurological symptoms is manifested by a return of normal sensation to the uppermost regions involved, with a gradual progression of this process downward. Objectively the improvement can best be followed in patients showing changes in vibration sensation, in whom the return of the sensation to lower and lower levels can be traced. It has been my impression that the cruder liver extracts (i.e., less potent extracts—not to be confused with diluted extracts) are more efficacious in the cases showing neurological changes. We do not deem it necessary to combine vitamins with liver to achieve optimal results. Once maximal improvement in the neurological

symptoms is reached, the same process of "weaning" may be followed as described above, but it is seldom possible to reduce the liver to amounts comparable to those sufficient for purely hematological types without a recurrence of symptoms

The administration of *hydrochloric acid* routinely is unnecessary. We employ it only when gastro-intestinal complaints persist, or appear in spite of adequate liver therapy. Fifteen to 30 drops (Diluted Acid Hydrochloridi, U S P) in half glass of water is either sipped with or is taken after meals. It is interesting that this almost insignificant amount (when compared to the normal gastric secretion) should result in the almost constant and striking relief that follows its administration.

The administration of *iron*, in addition to the liver extract, becomes necessary only when a concomitant iron deficiency develops. When this occurs it is first noted three to four weeks after the beginning of liver therapy and manifests itself as a gradually increasing hemoglobin lag and the development of a progressively lower color index. The red cell count levels off at about 4 million, with the hemoglobin at 60 per cent (10 gm), and remains there until iron is given. With this both the red cells and the hemoglobin rise to normal levels.

Complicating or coexisting diseases are treated just as if the pernicious anemia were nonexistent, remembering only that additional amounts of liver may be necessary.

A disconcerting complication, which occurs at some time in almost 10 per cent of patients treated for long periods, is the appearance of allergic reactions. These vary in severity from mild itching to shock and collapse. Changing the brand of liver will often suffice to eliminate reactions. If this fails, desensitization may be tried by the administration of increasingly larger doses beginning with extremely small amounts (such as  $\frac{1}{10}$  of a unit). Should this fail, two alternatives remain: the administration of oral instead of parenteral liver in the form of the liquid or dry extract, or the administration of stomach extract. Ordinarily certain practical objections exist which make the writer advise against the use of *oral extracts*. These may be summarized as follows: (1) eventual neglect of therapy due to lack of supervision, (2) greater cost, (3) greater difficulty in maintaining the blood at optimal level and (4) the development or progression of neurological signs and symptoms in spite of therapy.

Therapeutically, few diseases in the field of internal medicine are as satisfying to both the patient and his physician. The dramatic and spectacular improvement following the administration of liver is practically unequalled, and with the exception of the occasional inconvenience of liver injections, the patient continues with a normal life expectancy.

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## THE RH FACTOR\*

I DAVIDSOHN, MD, FACPT†

THE Rh factor is a property of human blood, the latest of a series of previously discovered blood factors. In order to understand the Rh factor, it will be necessary to review the other known properties of blood.

Since the discovery by Landsteiner of the first two blood factors, A and B, in 1901,<sup>1</sup> several additional factors have been discovered. Some are little known, others are known better but have assumed no importance in the practice of clinical medicine and surgery, though they are applied in the practice of legal medicine. This discussion will be concerned mainly with blood factors of interest to clinicians, especially in connection with blood transfusions.

### HEMAGGLUTINATION AND HEMOLYSIS

The frequently tragic results of early attempts at blood transfusion were due mainly to lack of knowledge of two reactions that may occur when the blood of two individuals of different species, and often when blood of two individuals of the same species, is mixed. One of these reactions is *clumping* or *agglutination* of the red blood cells of one individual by serum or plasma of the other. This special form of agglutination is called *hemagglutination* to differentiate it from other forms like bacterial agglutination. The second reaction is *laking* or *lysis* of the red cells by serum or plasma and is called *hemolysis*. The latter phenomenon, though of greater importance in blood transfusion reactions, is more complex than hemagglutination and more difficult to demonstrate. As hemolysis does not occur in the absence of hemagglutination, this discussion will be limited

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\* From the Department of Pathology, Mount Sinai Hospital.  
Parts of this paper have been condensed and reproduced from a monograph on Blood Groups, which is in the course of preparation.  
† Associate Professor of Pathology (Rush), University of Illinois College of Medicine, Director of Department of Pathology, Mt. Sinai Hospital.

to the latter except when special circumstances will require mention of hemolysis

Two elements are essential for hemagglutination the red cells which are clumped, the *agglutnogen*, and a substance in the serum or plasma which brings about the clumping, the *agglutinin*. The injection of red cells (the antigen) of one animal species into another leads to the production of agglutinating antibodies or *hemagglutinins*. They clump specifically the blood cells of the injected species

In addition to these agglutinating antibodies produced by immunization, or *immune agglutinins*, another type of hemagglutinins, not due to previous immunization, has been known as *normal hemagglutinins*<sup>2</sup>

The agglutination of red cells of one species by the serum of another was not surprising in view of other differences between species. Very startling was the discovery by Landsteiner<sup>1</sup> of agglutination of red cells of one person by the serum of another, both of them normal and healthy. Here for the first time individual differences were observed in the blood of members of the same species, *isoagglutination*, as contrasted with *heteroagglutination* or agglutination in mixtures of blood of different species. Even after Landsteiner's discovery there were reports in the literature referring to isoagglutination as a pathologic phenomenon, a manifestation of disease, and various authors claimed it to be a specific diagnostic test for a variety of diseases. Later studies confirmed Landsteiner's concept of isoagglutination as a normal physiologic phenomenon

#### BLOOD GROUPS

In experiments which led to the discovery of blood groups Landsteiner studied the behavior of mixtures of serum and of red cells of various persons. He found from the behavior of these mixtures that people could be divided in three groups: the largest group consisted of persons whose red cells were not clumped by serum of any other person, the red cells of a slightly smaller second group, and of a considerably smaller third group were clumped by certain serums. Landsteiner assumed the existence of two different agglutinable substances in the two last mentioned groups, factor A in the larger and factor B in the smaller group. He explained the failure of the red cells in the first mentioned, largest group to be clumped by the absence in

them of both of these factors and expressed it by the numeral "0." Later it became customary to refer to the "0" as a letter instead of a numeral

Corresponding to the factors in red cells there are agglutinins in the serum anti-A (also called "a" or  $\alpha$ ) reacts with factor A, and anti-B (also called "b" or  $\beta$ ) reacts with factor B

Factor A and anti-A cannot be present in the blood of the same person, nor can B and anti-B, as this would not be compatible with life This is expressed in *Landsteiner's law*. Every person has in his serum agglutinins that react with the factor or factors absent in his red cells Persons of group A have anti-B isoagglutinins, persons of group B have anti-A agglutinins, and persons of group O have anti-A and anti-B agglutinins

To these three groups a fourth, very rare group was added when a small number of persons was found whose red cells were clumped by the serums of persons belonging to the other three groups It was shown that the red cells of this group contain both factors, A and B, and it became known as group AB The serum of these persons lacks both anti-A and anti-B and does not agglutinate cells of any blood group

Distribution of blood groups varies in different races. In the white population in this country, about 45 per cent belong to group O, about 40 per cent to A, about 11 per cent to B, and about 4 per cent to AB

#### APPLICATION OF THE DISCOVERY OF BLOOD GROUPS TO BLOOD TRANSFUSIONS

It would seem that Landsteiner's discovery of differences in the properties of the blood and of incompatibilities arising therefrom should have been followed immediately by the practical application of this knowledge to blood transfusion This is indeed the prevalent opinion, even among those who are especially interested in blood transfusion. Actually, a study of the literature of the first decade of this century reveals a gap of several years during which one fails to find any clear evidence of a practical application of the discovery of blood groups

Hektoen was the first to recommend in 1907<sup>3</sup> the selection of compatible donors in order to avoid transfusion reactions His recommendation was that there be "selection of a donor whose corpuscles are not agglutinated by the serum of the recipient and whose serum does not agglutinate the corpuscles of

the latter [to avoid the danger of] erythrocytic agglutination within the vessels of the subject transfused" He suggested at the same time a simple procedure for cross-matching tests claiming that the actual isoagglutinative relation of the donor and the recipient is readily determinable. Hektoen's fundamental contribution to the safety of blood transfusions by the practical application of the knowledge of blood groups to the selection of compatible donors has been generally overlooked.

Landsteiner and Levine<sup>4</sup> discovered in 1926 two additional blood factors, M and N. About 30 per cent of the population have factor M, about 20 per cent have N, and the rest have both M and N, thus forming three types M, N, and MN. The term "blood types" is used in contradistinction to the "blood groups" A, B, AB, and O. The factors M and N play no part in relation to blood transfusions because there are no agglutinins against them in our blood normally, nor is a person of type N able to produce immune agglutinins against M when transfused with blood of type M or vice versa.

#### DISCOVERY OF THE RH FACTOR

The Rh factor was discovered in 1940 by Landsteiner and Wiener.<sup>5</sup> Rabbits were injected with the blood of the rhesus monkey (*Macacus rhesus*). Following a series of injections their serum clumped the red cells of the monkey, as was to be expected, but also the red cells of about 85 per cent of human beings. Landsteiner and Wiener accordingly assumed that there is a common antigenic factor in the blood of the rhesus monkey and of about 85 per cent of human beings. The factor was designated as Rh to indicate its relation to the animal species. The 85 per cent who have the Rh factor in their blood are called *Rh-positive*, the remainder are *Rh-negative*.

It was shown that the Rh factor is independent of the other blood factors. It occurs with the same frequency in persons of all groups and types, and is not related to sex. It differs from the factors A and B in several ways. There are no normal agglutinins against it, i.e., Rh-negative persons do not have in their serum agglutinins capable of clumping the blood of Rh positive persons.

Diamond<sup>6</sup> observed anti-Rh agglutinins in a child with nephrosis without a history of previous transfusions, but such instances must be extremely rare. Agglutinins capable of



clumping Rh-positive blood are due to immunization by the Rh factor and will be discussed later

The reference to factors A and B as blood properties is not entirely correct, because they are present not only in the blood but in tissues and in secretions, for instance saliva, of most persons of groups A, B, and AB. The Rh factor is found only in red blood cells. In both respects, in the absence of agglutinins against it, normally, and in its exclusive presence in red blood cells, the Rh factor is similar to the blood type factors M and N.

The rapidity with which the Rh factor became widely known is due to the fact that it helps to make understandable certain, previously unexplainable transfusion reactions, and that it has become the basis for a plausible hypothesis of the genesis of erythroblastosis foetalis.

#### COMMON ERRORS IN TYPING AND CROSSMATCHING

In the course of the years rules have been evolved governing the selection of safe donors for transfusions. The profession learned to recognize causes of errors and to guard against them in the typing of blood and in crossmatching tests. Some of these errors are due to the method of preparing reagents (typing serums, cell suspensions), some are due to the technic of the tests (temperature, speed of performance, bacterial contamination, and so forth), and some are due to inherent properties of the reagents (such as rouleaux formation, titer of agglutinins and irregular agglutinins). It is known that as a rule it is preferable to use donors of the same group as the patients, that the use of donors of group O (Moss IV) or so-called universal donors is to be restricted by various considerations which cannot be discussed in detail on this occasion. It has also been learned that crossmatching tests must be done before each transfusion.

The technic of transfusion has also been greatly improved, thus eliminating other sources of danger. The result of these advances has been that when a suitable donor was selected and when the transfusion was done according to established rules, there was good reason to expect that there would be no serious reaction.

#### THE RH FACTOR IN TRANSFUSION REACTIONS

In spite of all precautions, and in spite of using donors of the same groups as patients, instances of severe and even fatal trans-

fusion reactions\* have been known to occur. In some such cases a subsequent recheck of typing and of crossmatching failed to reveal any evidence of incompatibility. There was no explanation for these tragedies. They had to be dismissed as unexplainable accidents. When the donor and recipient were of the same group the cases are referred to as *intragroup transfusion reactions*.

Although there was no satisfactory explanation and no known means of avoiding such reactions, accumulated experience brought out two facts: (1) most of these reactions occurred in recipients who had received previously one or several transfusions without any reaction or with mild reactions and then the last transfusion was followed by a severe, usually hemolytic and sometimes fatal reaction, and (2) a smaller number of instances in which the first transfusion was followed by a severe or even fatal hemolytic reaction. Here too an interesting phenomenon has been observed. The majority of these reactions following a first transfusion occurred in *pregnant women*, usually during delivery or soon after childbirth or abortion.

Levine and Stetson<sup>7</sup> were the first to throw some light on the second type of these reactions when they reported in 1939 a hemolytic reaction in a woman who was given a transfusion following an abortion. The recipient and donor belonged to group O. Reexamination after the transfusion revealed the presence in the blood of the patient of an irregular agglutinin which clumped the blood of about 80 per cent of persons regardless of their blood group, even those of group O. Levine and Stetson suggested that the *irregular isoagglutinin* was the result of immunization of the patient in the course of pregnancy by an antigenic substance coming from the fetus. The substance was assumed to have been inherited by the fetus from the father and to have been transmitted from the fetus to the mother through the placenta. Later developments have shown the correctness of this ingenious hypothesis, although the discovery of the Rh factor was needed to furnish a complete explanation of the exact mechanism.

Shortly after the discovery of the Rh factor, Wiener and Peters<sup>8</sup> studied three cases of hemolytic transfusion reactions in patients

\* The most serious, so-called hemolytic reactions are characterized by hemoglobinemia, hemoglobinuria, icterus, oliguria with progressive azotemia, anuria, uremia and sometimes death.

who had received previously one or several transfusions without untoward manifestations. The recipients and donors were in the same group. An investigation of the serum of the recipients by means of an especially sensitive technic revealed the presence of an irregular agglutinin reacting with red cells of the donors and of about 80 per cent of persons, regardless of the blood group and including the usually inagglutinable group O. The irregular agglutinin in the patient was found to be similar to the agglutinin produced in rabbits by injection of rhesus blood. Both agglutinins clumped the cells of the same persons. The patients were shown to be Rh-negative, the donors whose blood was responsible for the reactions were Rh-positive and so were some of the donors whose blood was used in one or several of the previous transfusions.

Here was an obvious explanation of the transfusion reactions. The injection of Rh-positive blood into Rh-negative persons may be followed by development of anti-Rh agglutinins, just as it happened in the rabbits that were injected with rhesus blood.

There will be, of course, individual variations. Some Rh-negative persons will develop agglutinins after only one transfusion. Some will require several transfusions, and there may be persons who will not develop any demonstrable antibodies. After sensitization has taken place, the recipient and the donor, though of the same group, are not compatible any more as they had been before the recipient developed antibodies against the Rh factor.

The argument was clinched when Rh-negative recipients reacting unfavorably to transfusion of Rh-positive blood stood transfusions of Rh-negative blood without an untoward reaction and with the usual evidences of beneficial effects of successful transfusions. Thus the majority of severe transfusion reactions in recipients with a history of previous uneventful transfusions was explained by *Rh factor incompatibility*.

In some cases of such reactions, agglutinins against Rh-positive blood could not be detected in the serum of the recipient. Three possible explanations were offered<sup>9</sup> for their absence: (1) the tests were done too soon and the agglutinins were neutralized by the injected Rh-positive blood and a repetition of the tests after varying intervals of time revealed their presence in some instances; (2) the tests were done too late after the transfusion and the agglutinins have disappeared, as it is known to happen in other immunizations, (3) demonstrable agglutinins may not have been present in the circulating blood even before the transfusion—they may have been attached to the cells of the reticulo-endothelial system or their titer may have been too low to be detected by the available methods. The third explanation was substantiated by actual experience. Patients who developed hemolytic reactions fol-

lowing transfusion were found to be Rh-negative but did not show anti-Rh agglutinins on repeated examinations. The donors were Rh-positive. Transfusions with Rh-negative blood were free of reactions, while further transfusions with Rh-positive were followed by severe reactions.

The hypothesis of Wiener and Peters, confirmed by a long series of reports, can be accepted at the present time as offering an explanation for a majority of previously unexplained intra-group transfusion reactions and as furnishing means of avoiding many of them.

The second group of severe hemolytic reactions following first transfusions, as was mentioned, have been observed to occur mainly in *pregnant women* during or soon after delivery or after abortion. The application of sensitization by the Rh factor to the previously quoted case reported by Levine and Stetson<sup>7</sup> gave the clue for an explanation.<sup>10</sup> An Rh-positive husband of an Rh-negative wife may transmit the Rh factor to the fetus. Antigenic substances containing the Rh factor may pass from the fetus through the placenta to the mother and stimulate in her the development of anti-Rh agglutinins. If the mother needs a transfusion, the natural procedure would seem to be to use the husband as a donor if he belongs to the suitable blood group. It is obvious from our present knowledge, however, that the husband may be the least suitable donor, even if he is of the same group as his wife. If the foregoing situation regarding the Rh factor prevails and his blood is transfused, the result may be similar to that following a transfusion of incompatible blood—a severe or even fatal hemolytic reaction. Even if another donor is used instead of the husband, the chances are four out of five that the donor is Rh-positive and the result will be similarly disastrous.

A study of the blood of women who have suffered such transfusion reactions, of donors whose blood was responsible for them, and of babies (whenever that was possible) confirmed the existence of this immunologic state of affairs in a sufficiently large number of cases to permit the conclusion that this explanation is applicable to most instances of such reactions.

The questions may be asked at this point: *Why is it that cross-matching tests prior to these transfusions done with the usual methods failed to show incompatibility? Why did repetition of*

crossmatching tests, after the reactions had occurred, fail to reveal incompatibility.<sup>7</sup> The answer is that testing for the Rh factor and for anti-Rh agglutinins requires a special technic, more sensitive and delicate than tests for the usual isoagglutinins. The isoagglutinins anti-A and anti-B, which are used to detect the four blood groups, A, B, AB and O, have as a rule a higher titer than the anti-Rh agglutinins. They react within a wide range of temperature, from icebox temperature where the titer is at its peak, declining slightly through room and body temperature, and remaining detectable in most instances even at temperatures close to 50° C. Anti-Rh agglutinins react, as a rule, best at body temperature, and lose their strength rapidly with changes of temperature in either direction, so that at room temperature, at which the usual blood grouping and crossmatching tests are done, Rh-agglutination is in most instances difficult to detect or is even absent.

Rare instances have been reported<sup>8</sup> of anti-Rh agglutinins reacting better, or exclusively, at icebox temperature. The usual grouping and crossmatching tests are done on slides, Rh agglutination has to be carried in test tubes and requires prolonged sedimentation or centrifugation, which are known to favor all agglutination reactions. Thus it is apparent that the reason for the failure to discover Rh incompatibility prior to the introduction of the special sensitive technic was due to the usual methods of doing grouping and matching tests on slides and at room temperature, while Rh agglutination requires that the tests be done in test tubes at 37° C., and that the reaction be reinforced by fairly long incubation or by centrifugation.

#### THE RH FACTOR AND ERYTHROBLASTOSIS FOETALIS

After Levine had explained the transfusion reactions in pregnant women as due to sensitization of mothers by antigenic substances passing through the placenta from the fetuses, it was logical to consider the further consequences of this unique immunologic situation.<sup>11</sup> The placenta is a two-way road. If antigenic substances pass through it from the fetus and cause the production of antibodies in the mother with the resulting potential danger to her, the passage of these antibodies from the mother through the placenta may have a damaging effect on the fetus. This line of thought had been taken up in the past by several investigators. Darrow<sup>12</sup> came closest to what seems to be the solution of the problem when she incriminated chemical and antigenic differences in the hemoglobin of the fetus and mother as the responsible agents. She reasoned correctly that

the mother may be sensitized by the hemoglobin of the fetus, and that the antibodies thus produced may damage the child. The hypothesis was well conceived but lacked confirmation.

Levine's hypothesis substituted the Rh factor in the red cells of the fetus for the hemoglobin. Rh antibodies passing from the mother to the fetus damage its erythropoietic system and produce a hemolytic anemia and the other manifestations of the disease known as erythroblastosis foetalis.

Levine and his associates<sup>13</sup> checked this hypothesis by the simple means of comparing the incidence of the Rh factor in mothers of babies with erythroblastosis with that in the general population. Levine found about 90 per cent of them Rh-negative, while the incidence of Rh-negatives in controls was about 15 per cent. The husbands of these women and the babies afflicted with the disease were found to be Rh-positive in almost 100 per cent of cases, while the incidence of this property in the general population is about 85 per cent. Statistical data published by others<sup>14</sup> are in close agreement with Levine's.

It was found that many mothers of babies with erythroblastosis have anti-Rh agglutinins reacting with the blood of the baby. The serum of these mothers became the most important reagent for the detection of the Rh factor.

Two pertinent questions present themselves at this point. If erythroblastosis is based on the presence of the serologic condition of an Rh-positive father, an Rh-negative mother and an Rh-positive baby, *how can this hypothesis be reconciled with the finding of about 10 per cent of Rh-positive mothers in Levine's own series and with similar findings by other authors?* This can be answered by calling attention to the fact that fetal erythroblastosis is not a disease due to one specific cause, as for instance typhoid fever is due to the typhoid bacillus. It is in keeping with known facts about the disease that any agent capable of damaging the blood of the fetus and of producing a hemolytic anemia may start the chain of events that eventually produce the clinical syndrome known as erythroblastosis foetalis. Thus Rh antibodies are not the only agents capable of producing the disease, though apparently they are in most instances responsible. It is likely that various diseases of the mother may cause transmission of hemolytic substances to the fetus through the placenta and produce a result similar to or indistinguishable from fetal erythroblastosis. It is known that syphilis may do it. It is possible that other factors, thus far unknown, are operative.

The existence of antigenically differing fractions of the Rh factor has been demonstrated<sup>9, 15, 16, 17</sup> It is theroretically possible, though still to be proved, that a mother and her child may both be Rh positive but have different antigenic fractions. The mother may lack a fraction possessed by the child and thus become sensitized. It is therefore not necessary to construe the finding of Rh-positive mothers or of Rh-negative fathers or babies as in any way detracting from the validity of Levine's hypothesis The fact is that the hypothesis is applicable in about 90 per cent of the cases, and this is as good a corroboration as any hypothesis may be expected to furnish

The second question is *Why is erythroblastosis foetalis such a rare disease?* The question is justified by the discrepancy between the relative frequency of the combination of Rh-positive husband and Rh-negative wife (calculated to occur in about 13 per cent of marriages), and the reported rarity of the disease (quoted in statistics to be from 0.1 to 0.2 per cent of births). This contradiction is more apparent than real and it can be explained by a consideration of various factors which are involved in the mechanism of the genesis of the disease.

In the first place, an Rh-positive father does not have to transmit the Rh factor to his child The Rh factor of a person, his phenotype, is the result of inheritance from his parents He may inherit the Rh-positive property from both parents Then the formula of his blood is Rh Rh and he is homozygous, or he may inherit from one parent the Rh-positive property and from the other parent the Rh-negative property (designated as rh), and then his formula is Rh rh and he is heterozygous There is no test available for distinction of homozygous persons from heterozygous The child of a homozygous Rh-positive father will always be Rh-positive, while the child of a heterozygous father may be either Rh-positive or Rh-negative This mechanism cuts considerably the incidence of Rh-positiveness in children Kariher<sup>18</sup> reported recently erythroblastosis in one of twins who was Rh-positive, while the Rh-negative twin remained well

The next point has to do with the production of Rh antibodies in the Rh-negative mother of an Rh-positive child It does not follow that in each case of such a combination the mother must produce Rh-antibodies It is possible that passage from the fetus to the mother must be facilitated by an abnormally increased permeability of the placental barrier in order to permit the entrance of sufficiently large amounts of antigenic substances We know from experimental investigations in man and animals that active immunization depends on such quantitative factors This consideration is supported strongly by clinical evidence Erythroblastosis

foetalis is extremely rare in the first child. As a rule, one or more normal children precede the birth of a child with the disease. This may be interpreted as indicative of the need of several successive immunizations before the antibodies in the blood of the mother reach the level necessary to exert the destructive action in the child. In this connection it may be added that women may differ in ability to produce antibodies, as is known to occur in infectious diseases and in animal experiments.

The previously mentioned fact that the incidence of erythroblastosis increases with the number of pregnancies, suggests another factor contributing to the rarity of the disease—the tendency to limit the number of children in modern marriages. In Javert's series,<sup>19</sup> multiparity was associated with erythroblastosis in 92 per cent of the mothers. The disease is rare in primiparous women. It is interesting that in a case reported by Diamond<sup>6</sup> the mother of a first-born child with erythroblastosis had received eight transfusions prior to pregnancy. The last two transfusions were followed by hemolytic reactions.

After the antibodies have been produced in the mother in sufficient strength they have to pass to the baby. Here again the *permeability* of the placenta enters into the picture. It is possible that it has to be abnormally increased and the permeability in the direction from the mother to the baby may be of a different nature than in the opposite direction. Both may have to be increased to permit the working of the postulated mechanism, thus again limiting the frequency of the disease.

Finally, recent reports suggest that erythroblastosis may occur in *mild form*, (sometimes as a relatively mild hemolytic anemia) and that it may not infrequently escape recognition. This point will be taken up later in greater detail.

The factors just enumerated seem to me to be sufficient to account for the apparent discrepancy between the true incidence of the disease and the number of marriages between Rh-positive men and Rh-negative women.

Although Levine's hypothesis is strongly supported by statistical evidence, it is possible to conceive certain further corroborative observations.

1. An Rh-negative wife of an Rh-positive husband, mother of one or several children with erythroblastosis, may marry again, this time an Rh-negative man, and have with him healthy Rh-negative children.

2. An Rh-negative mother of Rh-positive children with erythroblastosis, wife of an Rh-positive man, may consent to arti-



ficial insemination from an Rh-negative donor and conceive normal Rh-negative children

3 An Rh-negative wife of an Rh-positive man may give birth to twins, one Rh-negative free of disease, the other Rh-positive suffering from erythroblastosis. The husband has to be, in such a case, heterozygous. The previously mentioned report of Kariher<sup>19</sup> is the first instance of this type.

### The Development of Manifestations of Erythroblastosis Foetalis

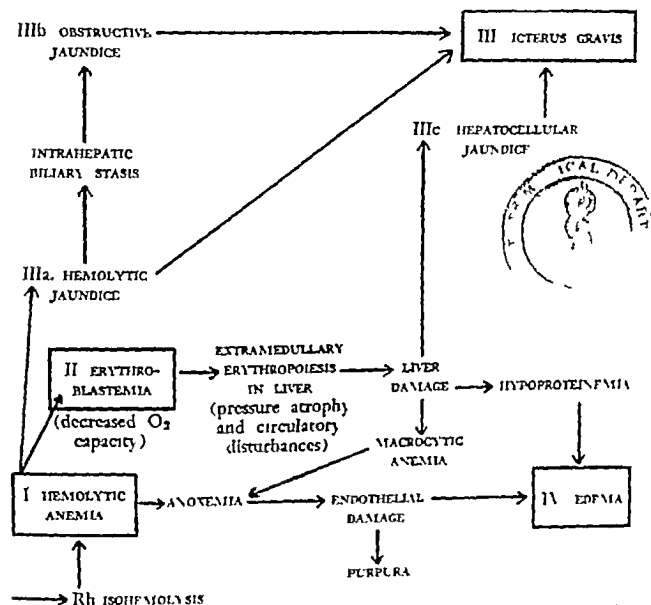
If it is agreed that Rh antibodies may produce hemolytic anemia in the fetus, how is the development of the other manifestations of the syndrome known as erythroblastosis foetalis to be explained? This is a question worthy of consideration in view of the heterogeneous manifestations of the disease of which the four most important ones are *hemolytic anemia*, *erythroblastemia*, *icterus gravis*, and *congenital hydrops*.

Figure 36 shows how these manifestations follow each other, step by step, in logical order. The results of hemolytic anemia are threefold: (1) *Anoxemia* (anemic anoxia) occurs as a result of a reduction of the oxygen-carrying capacity of the blood. (2) *Hemolytic icterus* develops from the destruction of blood and as a result of the presence of excessive amounts of components needed for formation of bile. This is an exaggeration of the normal tendency to jaundice in the newborn (*icterus neonatorum*). It differs from it by being present at birth (*icteric vernix caseosa*) or by appearing during the first day of life, while *icterus neonatorum* does not, as a rule, become manifest before the end of the second day. (3) *Erythroblastemia*, an abnormally increased number of nucleated red blood cells in the circulation, is a response of the bone marrow to hemolysis. The bone marrow of the newborn and of the child is known to respond to stimuli more intensely, quantitatively as well as qualitatively, than the marrow of the adult. It is known that nucleated red cells have a lower oxygen-carrying capacity than mature cells. A large number of such cells in the circulation adds to the anoxemia.

Each of the three results of hemolytic anemia leads to further developments, and these in turn are followed by others. The changes are frequently interconnected with one another. I hope that the chart (Fig. 36) will help to clarify this seeming maze.

In response to the anemia, *foci of erythropoiesis* develop in different organs. For the purpose of this discussion the most important are the *changes in the liver*. One finds frequently large masses of immature erythroblasts in the sinusoids compressing the liver parenchyma. In addition liver cells are frequently gorged with

hemosiderin and finally damage to the endothelium of the bile capillaries by the anemic anoxia adds the third factor leading to interference with normal hepatic function. Damaged liver function manifests itself in three ways, as shown in Figure 36. One is *hypoproteinemia*, the formation of blood proteins being one of the main



**PRINCIPLE** Rh positive husband of Rh negative woman transmits the Rh factor to the fetus. Rh antigenic substances pass from Rh positive fetus through placenta and produce in mother Rh antibodies. The latter pass from mother to fetus through placenta, act in the fetus as hemolytic agents, and start the sequence of interlocking pathologic changes as presented in this chart.

Fig 36—Pathogenesis of erythroblastosis foetalis

functions of the liver. Hypoproteinemia, in turn, leads to *edema*, which has the oldest history of all manifestations of erythroblastosis, having been known for centuries as congenital hydrops. The other result of hepatic damage is a *hepato-cellular type of jaundice*, which tends to intensify the previously mentioned hemolytic jaundice. Liver damage is known to be associated with *macrocytosis*, which

is present in erythroblastosis<sup>20</sup> Macrocytes are less efficient carriers of oxygen than normocytes and so contribute to the anoxemia, similar to erythroblasts

The anoxemia, the development of which we have traced from at least three sources, hemolytic anemia, erythroblastemia, and macrocytosis, results in *endothelial damage*, which is responsible for three types of changes. It causes edema, thus acting synergistically with the hypoproteinemia. Endothelial damage explains the purpura, an occasional complication of the disease. Finally, the damage to the endothelial lining of biliary capillaries together with the stasis of bile due to hemolytic jaundice contribute to formation of bile plugs in the liver which lead to intrahepatic biliary obstruction and to obstructive jaundice. Thus we have now the third element in the formation of the severe jaundice of erythroblastosis, the *icterus gravis*.

The chart makes it clear, I hope, why *edema* is the most serious manifestation of erythroblastosis and the least frequently reversible. That is the reason why infants with generalized congenital hydrops recover so rarely. In Javert's<sup>19</sup> series the mortality was 100 per cent. Anemia and erythroblastemia are usually most pronounced in this form, jaundice may be masked by edema.

*Icterus gravis* is next in seriousness, with a mortality of 54 per cent (Javert). It is likely that its seriousness and the chances of recovery may depend on the associated liver damage. It is justifiable to conclude from the chart and in keeping with clinical experience, that hemolytic anemia may be present as the only manifestation of the disease, with or without excessive erythroblastemia. If mild, it may be overlooked entirely or it may not be interpreted as a manifestation of erythroblastosis. The suggestion has been made that the disease would be better called hemolytic disease of the newborn<sup>21</sup>. The suggestion has much in its favor, as hemolytic anemia is the basic change in the disease and erythroblastemia is a less significant finding.

There is a tendency in recent publications to consider every case of *hemolytic anemia of the newborn*, even when it is moderate or mild, and even without erythroblastemia or jaundice, a manifestation of, and synonymous with erythroblastosis, especially if the distribution of the Rh factor in the family is of the type characteristic for erythroblastosis, father and child positive, mother negative. This is an extreme view likely to lead to inclusion of cases which have nothing to do with erythroblastosis with resulting confusion. No student of the subject will deny that there are instances of hemolytic anemia of the newborn which are not erythroblastosis foetalis. Septic infections, neonatal and prenatal bronchopneumonia

may be associated with severe hemolytic anemia. It is sometimes extremely difficult and even impossible to diagnose the underlying infection clinically. Only an autopsy may reveal it.

The diagnosis of erythroblastosis is not always easy, especially in mild abortive cases, and an autopsy may be essential for a definite diagnosis. There are instances in which even autopsy findings may not be unequivocal, especially in premature infants and in stillbirths. In such cases a study of the Rh factors in the parents and child and of anti-Rh agglutinins in the mother may be of considerable help in arriving at a correct interpretation. It has already been stated that this cannot be relied on too implicitly and I have had one example of an Rh positive husband of an Rh-negative mother of a perfectly healthy Rh-positive infant, with well developed anti-Rh agglutinins in the mother. Levine<sup>15</sup> reported similar findings in two women.

#### Illustrative Cases

Two cases will be quoted to illustrate the role of tests for the Rh factor in obscure blood disease in infants.

**CASE I**—A five-month-old white girl, patient of Dr. E. Padnos, was admitted on July 12, 1943, suffering from a severe anemia, with a history of jaundice at birth lasting for over a month. The child did not thrive well and passed bloody stools on several occasions. She was very pale. The spleen and liver were palpably enlarged.

The accompanying tabulation summarizes some of the blood findings. The differential blood smears showed marked macrocytosis, moderate anisocytosis, poikilocytosis and hyperchromia, and slight polychromatophilia. The reticulocytes were 3.6 per cent, platelets 108,000, coagulation time nine minutes, bleeding time over ten minutes, icterus index 11 and 13. The fragility test showed normal values. Serologic tests for syphilis were negative.

In view of the history of jaundice at birth and of the severe anemia, hemolytic disease of the newborn was considered. The father and the child were B Rh-positive, the mother O Rh-negative. There were no demonstrable anti-Rh agglutinins in her serum. The father was used as donor in both transfusions. The use of an Rh-negative donor was not considered necessary in view of the age of the child. Any antibodies that the child may have had at birth would have been eliminated by this time.

The child left the hospital eighteen days after admission very much improved, and has remained well since.

## TABULATION

BLOOD FINDINGS IN A YOUNG INFANT WITH SEVERE ANEMIA, ENLARGED LIVER AND SPLEEN AND A HISTORY OF ICTERUS NEONATORUM

Date 1943	R B C	Hb		W B C	Neutro- phils %	Eosino- phils %	Lympho- cytes %	Mono- cytes %	Normo- blasts*
		Gm	%						
7/13	1,110,000	4.8	28.8	21,900	28	4	64	2	15
7/14	1,390,000	5.0	30.0	22,900	22	—	74	2	20
Blood Transfusion, 125 cc									
7/15									
7/16	3,380,000	10.0	60.0	10,350	30	2	64	4	—
7/20	3,200,000	10.4	62.4	7,000	26	6	66	2	22
Blood Transfusion, 100 cc									
7/23									
7/26	3,630,000	11.9	71.4	7,000	15	3	79	3	—
7/29					29	1	64	6	—

\* Per 100 white blood cells

Was this a case of erythroblastosis foetalis? The history of prolonged jaundice at birth, the clinical picture and hematologic findings would fit into that diagnosis. Purpura is not infrequently observed as a complication. The prompt response to transfusions is also more commonly seen in this disease than in other blood disorders. Finally, the Rh formula in the family is in favor of the diagnosis of late erythroblastosis foetalis with purpura.

Another diagnostic problem presented itself in Case II.

CASE II—A five-month-old girl, patient of Dr. B. M. Gasul, was admitted with a history of extreme restlessness with rigidity of the body and retraction of the head for the past two months. The weight at birth was 8 pounds and was the same on admission. The child was born at term, the delivery was spontaneous. The mother stated that the child became jaundiced at the age of four days and that jaundice persisted for two months.

The red blood count was 4,830,000 and 5,380,000; the hemoglobin was 15.4 gm (92.4 per cent) and 14.9 gm (89.4 per cent). The other findings including the differential blood count were not remarkable. Serologic tests for syphilis were negative.

In the course of blood grouping and crossmatching tests it was found that the serum of the mother clumped cells of groups A, B, O and AB, though she was of group AB. Serum of group AB should not clump cells of any group. It was established that she was Rh-negative and had strong anti-Rh agglutinins, that her husband was A Rh-positive, and that the child was AB Rh positive. This was the third child in the family, the first, a girl five years old, was normal, the second a three-year-old boy was jaundiced at birth but had been well since.

In the differential diagnosis between birth injury and a residual involvement of the central nervous system with Kernicterus due to icterus gravis, the serologic findings of an Rh formula typical for erythroblastosis foetalis and of anti-Rh agglutinins in the mother favored the last mentioned diagnosis.

Kernicterus with spastic manifestations and evidence of mental deficiency has long been considered a late complication of icterus gravis. This case shows the value of Rh tests in such cases. In view of the opinion that some forms of juvenile cirrhosis may be another residual condition after erythroblastosis, as a result of severe hepatic damage, studies of the Rh factor in such families may be of interest.

## TESTING FOR THE RH FACTOR

Testing for the Rh factor may be done either with animal (guinea pig) or with human immune serum. The serum of guinea pigs, immunized with rhesus blood, may show significantly higher titers for Rh-positive blood.

Human serum with anti-Rh agglutinins may be obtained, rarely, from Rh-negative patients who had received repeated transfusions of Rh-positive blood, and more frequently, though still rarely, from Rh-negative mothers of babies with erythroblastosis.

For technical details regarding preparation of animal serums and their uses, detection of anti-Rh agglutinins in human serums and their uses, elimination of interfering isoagglutinins, crossmatching tests for Rh incompatibility, which can be done without available anti-Rh serums, the interested reader is referred to the bibliography<sup>8, 9, 16, 17, 22, 23</sup>

## PRACTICAL APPLICATIONS

## Repeated Transfusions

Patients who are receiving repeated transfusions may benefit by having their blood tested for the Rh factor. If it is found negative and if Rh-negative blood is available it is advisable to use it for two reasons: reactions will be avoided if the patients have become sensitized previously, otherwise sensitization will be prevented. Experience has shown that severe hemolytic reactions in patients receiving repeated transfusions have, as a rule, been preceded by mild or moderate reactions which have been disregarded. The lesson from this is to test for the Rh factor the patient who is receiving repeated transfusions and in whom a reaction, especially with hemolytic features, has been observed.

It should be noted that the sensitive crossmatching technique for Rh incompatibility may give a patient in need of transfusion a measure of protection even if Rh tests are not done.

## Transfusions in Pregnancy

Pregnant women, or those recently pregnant, should receive the benefit of the new knowledge. They are especially in danger if there is a so-called bad obstetrical history of previous births of babies with edema, jaundice, and of stillbirths. Rh-

negative donors are to be used, of the same group as the patients, or of group O. The latter when Rh-negative are better than Rh-positive ones, even of the same group as recipients. The husband should not be used, unless expert serologic tests have eliminated any evidences or even possibility of isoimmunization during pregnancy.

#### Transfusion Therapy in Erythroblastosis Foetalis

Transfusion is the therapy of choice for newborn children with any manifestations of erythroblastosis. It is important that blood be given as early as possible and that indications for further transfusions be controlled by the condition of the child. It is essential that Rh-negative blood be given, although the infants are Rh-positive. It is assumed that they may have some of the anti-Rh antibodies in their circulation or attached to the reticulo-endothelial system, ready to react with injected Rh-positive blood. If known Rh-negative blood is not available the next best course is to use the mother's blood cells, after the plasma is removed and the red cells washed twice with sterile saline and resuspended in sufficient saline to make up for lost volume. This is always a safe procedure because an infant never has isoagglutinins in his serum directed against the cells of his mother.

It has been recommended that mothers be not permitted to nurse infants with erythroblastosis, because anti-Rh agglutinins have been found in breast milk.<sup>4</sup>

The results of prompt transfusion therapy in erythroblastosis have been extremely gratifying. Javert<sup>19</sup> reported a drop in mortality from 73 per cent to 14 per cent since 1941 in his series. This success is especially significant in view of the fact that erythroblastosis has been listed as responsible for 3.2 per cent of fetal and infant mortality.

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# THE RH FACTOR IN OBSTETRICS

EDITH L. POTTER, M D, Ph D \*

THE discovery of the Rh factor and its correlation with clinical material has led to the establishment of an etiologic basis for certain intragroup transfusion reactions and for erythroblastosis foetalis, two conditions the cause of which had previously been unknown. Both are extremely important in the practice of obstetrics because of the large number of transfusions given in the immediate postpartum period, and because of the poor prognosis for future childbearing in a woman who has once given birth to an infant suffering from erythroblastosis. A relationship between transfusion reactions in the mother and erythroblastosis in the offspring was first recognized by Levine, Katzin and Burnham<sup>1</sup>. In the short time that has elapsed since their observations were made, much clinical data has been accumulated which substantiates their findings, and gives a broader understanding of the processes involved.

## GENERAL CHARACTER OF THE RH FACTOR

The Rh factor is an antigenic substance present in the red blood cells of 85 per cent of the white population of the United States<sup>2</sup> and England<sup>3</sup>. It was discovered by Landsteiner and Wiener<sup>4</sup> in 1940, who found that rabbits inoculated with red blood cells from the monkey, *Macacus rhesus*, produced antibodies capable not only of agglutinating the blood cells of the *Macacus rhesus* but also the cells of a large number of human beings.

It was thus evident that rhesus blood and most human blood contained a common antigenic factor, which, because of the association of the monkey with its discovery, was designated Rh. Those individuals whose blood contained the antigen and would react with the rabbit serum were considered Rh-positive.

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\* Assistant Professor of Pathology, Department of Obstetrics and Gynecology, University of Chicago School of Medicine, Pathologist, Chicago Lying-in Hospital

(Rh+) while those whose blood failed to react were considered Rh-negative (Rh—)

The presence or absence of the Rh factor is in no way related to sex or to the other previously known blood groups A, B, O and M, N. It is like M and N insofar as isoagglutinins against it are never normally present, and differs in this respect from A and B, for which isoagglutinins are always present except in AB individuals who possess both antigens (anti-B agglutinins in A individuals, anti-A in B individuals, anti-A and anti-B in O individuals). However, unlike M and N, isoagglutinins may be produced by the introduction of Rh-positive cells into the circulation of an Rh-negative individual.

The Rh factor appears to be limited to red blood cells and is not present in other body tissues and fluids. A and B, on the other hand, are disseminated widely throughout the body in the majority of all individuals. In some (about 20 per cent who are termed "nonsecretors") A and B are also found only in blood cells. The possibility of the transmission of the Rh antibody to breast milk has been considered, but to date has been demonstrated in only one case<sup>5</sup>.

Like the other blood groups, the Rh factor is inherited as a mendelian dominant. It involves a pair of allelomorphic genes Rh and rh, Rh (Rh-positive) being dominant over rh (Rh-negative). Both the genotypes Rh Rh and Rh rh will be Rh-positive, while only the genotype rh rh will be Rh-negative. Assuming random mating, 36.9 per cent of the population is Rh Rh, 47.7 per cent Rh rh, and 15.4 per cent rh rh. It would be possible for two heterozygous Rh-positive parents to have an Rh-negative child, but impossible for two individuals who are Rh-negative to have an Rh-positive child. This fact is of medico-legal significance in the establishment of parentage, and of genetic interest in relation to the diagnosis of single and double ovum twinning.

The Rh factor, like A and B, is not uniform in distribution in different races. Relatively few studies have so far been made but these indicate the incidence of Rh-positive individuals is much higher among American Indians<sup>7</sup> and Chinese<sup>8</sup> living in

<sup>5</sup> Witebsky and Heide (*Proc. Soc. Exp. Biol.*, 52 '80) have subsequently reported two additional cases. A high titer of agglutinins has also been demonstrated by I. Davidsohn in the breast milk of a patient delivered of a baby with erythroblastosis at the Chicago Lying-in Hospital.

this country and somewhat higher among the American Negroes<sup>9</sup> than among the remainder of the population. Only one Rh-negative individual was found among 169 reputedly full-blooded Indians, and in Indians of mixed parentage the incidence of Rh-negative individuals was halfway between that found for white and for full-blooded Indians. It has been postulated for Rh as well as for A and B that early mutation from the O and the Rh-negative state plus geographical segregation is probably responsible for the present proportions of individuals with A, B, O blood groups as well as for those who are Rh-positive and Rh-negative<sup>6, 10</sup>.

#### RELATION TO TRANSFUSION REACTIONS

Prior to the discovery of the Rh factor in 1940, occasional cases had been reported in which severe or fatal transfusion reactions had occurred despite the use of blood of the same group, and many more had been observed which had not been reported. It was presumed that these were due to atypical agglutinins or hemolysins and in a few cases such antibodies were demonstrated. Anti-M agglutinins were found in five cases,<sup>11</sup> and the majority of the other reactions appear to have been probably due to anti-Rh agglutinins.

Levine and Stetson<sup>12</sup> in 1939 demonstrated an agglutinin in the blood of a patient recently delivered of an extremely macerated fetus which reacted with approximately 85 per cent of the bloods with which it was tested and they postulated that the retention of the dead products of conception had immunized the mother. The experimental antibodies produced by Landsteiner and Wiener<sup>4</sup> and reported in 1940 were found to be almost identical in their reaction to those from the patient of Levine and Peters. Although the terminology is based on the experimental animal work, the first demonstration of the Rh antibodies was actually clinical.

The explanation of these intragroup reactions due to Rh immunization is based on the fact that, although antibodies against the Rh factor are not normally present, they may be produced in susceptible Rh-negative individuals by the introduction of Rh-positive cells into their blood stream. It is believed that this introduction of cells may be accomplished either through the administration of Rh-positive cells by transfusion, or by the transfer of fetal Rh-positive cells to the maternal

circulation during pregnancy. It has been presumed that a pathologic state must exist and that a break in the placental vessels necessary for the entrance of cells into the maternal blood stream. Kariher<sup>13</sup> suggests, however, that a physiologic intra-uterine destruction of red blood cells may cause a breakdown of the hemoglobin into molecules small enough to pass through the intact placenta, but large enough to retain their antigenic capacity.

In either case, the mother, in order to become immunized during pregnancy, must be Rh-negative, the father must be Rh-positive, the fetus must inherit the Rh-positive character from the father. The fetal cells or their antigenic components must enter the maternal circulation. The maternal organism must be capable of reacting and producing antibodies.

After anti-Rh agglutinins have once been produced and the patient has become sensitized to the Rh factor, the subsequent introduction of Rh-positive blood, even though it is of the same major blood group, will be followed by agglutination of the donor's Rh-positive cells by the recipient's anti-Rh agglutinins. The reaction between Rh-positive cells and anti-Rh agglutinins can be as disastrous as it would be between group B cells and anti-B agglutinins if blood of a group B donor were given a group A patient.

Probably the majority of Rh-negative individuals have, in the past, been given Rh-positive blood when they have been transfused, and it seems somewhat strange that evidence of the production of antibodies has not been more frequent. The amount of blood, the number of injections and the time interval between injections necessary to produce antibodies in the human are not known but it appears that even with multiple transfusions conditions are not often optimum for antibody formation.

It is also true that individuals vary in their capacity to produce antibodies, and that the antibody-stimulating capacity of various antigens differ. It is probable that, in the majority of Rh-patients who receive more than one transfusion, the transfusions are either too close together or too far apart to be effective in antibody production.

During pregnancy, however, a chance for the continued introduction of Rh-positive cells into the circulation exists for a period of several months. The Rh antigenic property appears very early in fetal life and was present in five fetuses examined

by Bornstein and Israel,<sup>14</sup> the youngest being 13 cm. in length. Transfusion reactions due to anti-Rh agglutinins consequently appear more commonly in women who have been pregnant, and especially in those whose infants have given evidence of being affected by the antibodies, than in nulliparous women, or men.

### RELATION TO ERYTHROBLASTOSIS

Many years before the discovery of the Rh factor it had been postulated that maternal immunization against the products of conception, particularly when the fetus was of a blood group incompatible with that of the mother, might be responsible for maternal toxemia or for infant or fetal death. It was felt that this was especially apt to be true in those cases where the latter was associated with jaundice in the offspring.<sup>15</sup> Many papers had appeared on erythroblastosis and numerous suggestions had been put forth as to its etiology. Macklin<sup>16</sup> had attempted to show a definite hereditary tendency but was unsuccessful. Two facts which were known from clinical experience had to be taken into account in arriving at any conclusion regarding etiology. These were (1) the rare occurrence of the disease in first pregnancies, and (2) the almost constant repetition in all subsequent pregnancies after the disease had once occurred. Darrow,<sup>17</sup> after reviewing the literature dealing with erythroblastosis and considering all the possibilities, concluded that the only explanation sufficient to explain its etiology in view of known facts was that the disease was a response on the part of the fetus to antibodies which it had been responsible for producing in the mother.

### Outline of Theory

The early clinical investigations of the Rh factor revealed that the majority of the patients in whom antibodies similar to those of Landsteiner and Wiener could be found had not only been recently pregnant, but had given birth to infants with erythroblastosis. As a result of this, the blood of all available women who had given birth to such infants was examined and a very high percentage were discovered to be Rh-negative, in contrast to the low percentage in the general population. It was therefore concluded that the manifestations of erythroblastosis were probably due to the action of maternal antibodies on the fetus.<sup>1</sup> The theory of etiology is based on the fact that when an Rh-negative

woman married to an Rh-positive man conceives an Rh-positive child, the Rh-positive blood cells from the fetus may pass through the placenta and produce anti-Rh agglutinins in the mother. These, in turn, pass back through the placenta to the fetus and cause the hemolysis of fetal cells which is characteristic of erythroblastosis.

Sufficient evidence has accumulated to put this theory on a firm basis. It appears that at least 90 per cent of all women giving birth to infants with erythroblastosis are Rh-negative, that practically all fathers, and all infants themselves, are Rh-positive. Anti-Rh agglutinins, however, cannot be demonstrated in a fairly high percentage of women giving birth to infants in whom the diagnosis of erythroblastosis has been definitely established. They are more apt to be demonstrable one to two weeks following delivery than at any other time. Levine and his co-workers<sup>2</sup> found them within two weeks after delivery in about 50 per cent of their patients, after two months in only 10 per cent. They have been observed, on the other hand, as late as six years following the last pregnancy.<sup>18</sup>

It is believed that, in those patients whose blood does not contain demonstrable agglutinins, the agglutinins are fixed in the reticulo-endothelial system and although capable of exerting a harmful influence on the fetus they are not free in large enough numbers to be detected. In approximately 12 per cent of all marriages the wife will be Rh-negative, the husband Rh-positive. About 9 per cent of all pregnant women are Rh-negative and give birth to Rh-positive offspring. The potential set-up for erythroblastosis is thus present in almost one out of ten pregnancies, but is actually manifest in only one in four hundred or more. The principal reason why it does not occur with greater frequency is probably because except in rare instances the placenta remains intact and does not permit the escape of fetal cells. Differences in antigenic capacity of the fetal cells and the antibody-forming activity of maternal tissues may also influence the incidence of the disease.

**In the Light of This Theory, Why Do Some Rh positive Women Give Birth to Infants with Erythroblastosis?**

The 10 per cent of women with infants having erythroblastosis who are Rh-positive fail to meet the requirements for this theory. There are four possible explanations that an error has been made



in performing the agglutination test, that the diagnosis of erythroblastosis is in error, that antigens other than the Rh can cause isoimmunization of the mother, that erythroblastosis cannot be considered an entity, but is a clinical syndrome capable of being produced by various etiologic agents

At times all of these conditions seem to act, the first two, I believe, being more often responsible than the others. In a series of Rh determinations reported by Potter, Davidsohn and Crunden,<sup>18</sup> six of sixty women giving birth to infants on whom a diagnosis of erythroblastosis had been made, were Rh-positive, the remainder Rh-negative. Five of these six infants were badly macerated and the diagnosis was based on moderate enlargement of spleen and liver, edema greater than that usually due to maceration and evidence of an increase in nucleated cells in the clots within the blood vessels of various organs. The tissues were too badly degenerated to permit detailed histologic examination. In each case this was the only fetus affected and none of these women have been subsequently pregnant. Although these are still being considered cases of erythroblastosis it is entirely possible, especially in view of the Rh-positive status of the mother, that the diagnosis is in error.

In the fifth case, however, there was no doubt that erythroblastosis existed. The mother had had three normal children followed by three pregnancies ending in the delivery of three stillborn fetuses all of which were examined at autopsy and in whom the diagnosis of erythroblastosis was definitely established. This case formed the principal stumbling block to my complete acceptance of the theory of Rh isoimmunization as the cause of erythroblastosis. The patient's blood was examined early in 1941 when work on this problem was first being commenced. A single serum which had had specific antibodies absorbed with purified saliva was used. She subsequently became pregnant and delivered a full term female infant in August, 1943. The cord blood showed 91 nucleated red blood cells per 100 leukocytes an icterus index of 22, and hemoglobin of 14 gm. The child became deeply jaundiced within a short time of birth and the icterus index rapidly rose to 138. It was transfused several times and although alive at five months of age has evidence of a definite kern-icterus.

The blood of the mother was again tested early in this last pregnancy and she was discovered to be Rh-negative. Subsequent testing with eight different immune serums all of which have given uniform results, establishes an error in the original diagnosis, and instead of being Rh-positive she is actually an Rh-negative individual. The blood of this patient has been examined several times during pregnancy and the puerperium. She has always been found Rh-negative but anti-Rh agglutinins have never been demonstrated.

These six cases which were reported as Rh-positive show that some error in laboratory technic was responsible for one such diagnosis, and that possibly the condition was not erythroblastosis in the other five.

In further support of the possibility that an error may be made in the diagnosis of the disease is the fact that all infants with generalized edema, pleural and peritoneal effusions are, by the majority of investigators, included under the term 'fetal hydrops' which in turn is considered synonymous with erythroblastosis. I<sup>10</sup> have recently called attention to the fact, however, that fetal hydrops frequently occurs in the absence of erythroblastosis. Seventeen such fetuses had been observed, and since the publication of a paper on the subject, an eighteenth has been added. Despite excessive accumulations of fluid none of these infants has shown histologic evidence of erythroblastosis. The twelve mothers on whom it was possible to do Rh determinations were all positive, four of these women have subsequently given birth to normal infants.

Gallagher and his associates<sup>20</sup> selected twenty women who had given birth to infants with erythroblastosis, the term being used, according to the authors, in the 'broad sense of Diamond, Blackfan and Baty.' Insofar as can be determined from the paper, the presence of jaundice in the infant was the only criterion demanded for the diagnosis. They found nine of these mothers Rh positive and conclude on this basis that Rh determinations of the mothers are of no value in establishing the diagnosis, and that since such a large proportion are Rh-positive, the theory of etiology cannot be sound.

This appears to be another example of inaccurate diagnosis. It is unfortunate that the authors were not more specific as to the criteria on which the diagnoses were based. Jaundice in the newborn, however, is by itself no proof that the infant has erythroblastosis. In my experience there have been no cases of erythroblastosis in which all features were typical and the diagnosis could be established beyond doubt in which the mother was Rh-positive.

The third possible explanation—that antigens other than the Rh can cause immunization of the mother—is believed by Levine to account for the 10 per cent incidence of Rh-positive women in his series. He, as well as other investigators, believes that erythroblastosis in these cases is due to the action of other isomune bodies in some instances anti-A or anti-B (when the fetus is of a blood group incompatible with that of the mother) or to immune bodies produced by antigens not yet identified. One such possible antigen he has designated Hr.<sup>21</sup>

The fourth possibility—that erythroblastosis is not an entity, but a clinical syndrome capable of being produced by various etiologic

agents—is a contention which had been put forth on numerous occasions prior to the discovery of the Rh factor. It is well known that other conditions, especially sepsis and atresia of the bile ducts, may cause severe illness and jaundice, sepsis and syphilis may both cause marked splenic enlargement, an increase in nucleated red blood cells beyond the limits usually considered normal for the newborn is found not infrequently in babies who are ill from almost any cause, excessive edema usually designated “fetal hydrops” may be entirely unassociated with true erythroblastosis.

If any one of these single characteristics is considered a sufficient basis for the diagnosis of the disease, then erythroblastosis is certainly not a specific entity. However, this seems entirely unjustifiable, for there is a definite syndrome which is characteristic of this disease and none other. There are mild and borderline cases, as there are in almost any disease, in which a positive diagnosis may be impossible. It is better, however, to recognize this fact than to say definitely on insufficient grounds that the disease does, or does not, exist.

#### *Importance of a Correct Diagnosis*

Few investigators who have reported Rh determinations have given the basis for the diagnoses of erythroblastosis in the cases they have examined. Since there appears to be a considerable diversity of opinion in the minds of different individuals as to what should be included under this term, it would be extremely interesting if full clinical and pathological reports on all infants who supposedly have erythroblastosis whose mothers are Rh-positive could be published. It would give a much better idea as to the etiologic role which must be ascribed to some other antigen or etiologic agent.

The establishment of a correct diagnosis of erythroblastosis is important in relation to prognosis for future pregnancies. Among fifty women observed by me who have had fetuses or infants die of erythroblastosis, twenty-two have had thirty-seven subsequent pregnancies and all of these infants have had erythroblastosis. Only three have survived. This incidence of repetition in subsequent pregnancies is higher than has been reported by some other investigators, but in any series it is sufficiently high to make the outlook for future childbearing very unpromising.

In questionable cases the Rh status of the father, mother and affected infant may lend support toward the establishment or rejection of the diagnosis of erythroblastosis. It, in itself, how-

ever, is never sufficient ground for making the diagnosis. Unless there is some definite clinical or pathologic evidence that the disease exists the diagnosis should not be made.

#### TREATMENT OF ERYTHROBLASTOSIS

The treatment of an infant born alive with erythroblastosis is *transfusion with Rh-negative blood*. In the group who do not show an appreciable anemia at birth, transfusion still seems to improve the chance of survival. The infant appears to be benefited by the introduction of cells which are incapable of being affected by the antibodies producing the disease. Anti-Rh agglutinins in the infant's blood have been demonstrated in only one instance, but despite this fact Wiener has shown that Rh-negative cells persist in the circulation longer than do Rh-positive cells.<sup>22</sup>

The fragility of cells and bleeding and coagulation time are often normal in erythroblastosis. Despite this, many infants with erythroblastosis show some evidence of hemorrhage, and it is probably wise to administer vitamin K even though it has no therapeutic value in the prevention of hemolysis. Intramuscular or intraperitoneal injections of blood will in no way compensate for failure to transfuse. Other forms of medication have not yet been proved of value in the treatment of this condition. It has been suggested that in women who have previously given birth to infants with erythroblastosis, the artificial termination of pregnancy one to two months prior to the expected date of confinement might be advisable. This suggestion is based on the belief that the longer a fetus is subjected to the harmful effects of maternal antibodies, the more severe the disease will be. These infants, however, are subjected to the influence of these antibodies very early in intra-uterine life and it seems that the handicap of prematurity more than offsets any advantage which may be gained by removal of the infant from the influence of the anti-Rh agglutinins. An exception to this might be in those cases in which agglutinins are demonstrable for the first time late in pregnancy, or in which at this time the titer shows a marked increase.

#### PREVENTION OF TRANSFUSION REACTIONS

Although by far the greatest loss of life resulting from maternal isoimmunization is in the fetus, a preventable, and there-

fore more important, loss is to be found in relation to transfusion reactions in the mother.

Any Rh-negative woman who is, or has been pregnant, or who has had previous blood transfusions may have anti-Rh agglutinins in her body. They may, in rare instances, be demonstrable during or after pregnancy even though the infant remains normal. On the other hand, even though their existence is proved by the effect they produce on the infant they may never be demonstrable by any *in vitro* agglutination test. This means that all women who are or have been pregnant should, ideally, have their Rh status determined and, if found to be Rh-negative be given only Rh-negative blood.

If it becomes possible to develop a satisfactory testing serum in laboratory animals, the day may well come when Rh determinations are a routine part of all pretransfusion examinations, and when all Rh-negative individuals will be given only Rh-negative blood. At the present time human serum containing anti-Rh agglutinins forms the greater part of the testing serum which is in use. This is extremely limited in amount and consequently the number of determinations which can be made are relatively few in number. It is impossible to test all pregnant or puerperal patients and in very few clinics is it even possible to test all individuals requiring transfusions. Since it is definitely believed, however, that women giving birth to infants with erythroblastosis possess an antibody even though it cannot be demonstrated, all such should be transfused with Rh-negative blood.

In the absence of serum for routine testing of pregnant or puerperal patients, it is advisable before giving a transfusion to such a patient to cross match the donor's cells and the patient's serum for one hour at  $37^{\circ}\text{C}$  and proceed in the manner recommended by Levine<sup>23</sup> and others<sup>24, 25</sup>. The anti-Rh agglutinins fall in the category of so-called "warm agglutinins" which react only at body temperature. For this reason they may be missed if the tests are performed at room temperature. Although it is theoretically possible for reactions to occur even though matching at  $37^{\circ}\text{C}$  indicates compatibility, such reactions are extremely rare in actual practice. If reactions do occur they are usually of mild or moderate degree and are almost never fatal. It has been shown that the administration of large doses of alkaline drugs aids in preventing precipitation of hemoglobin in the kidney.

tubules, and in case Rh-positive blood is inadvertently given an individual possessing anti-Rh agglutinins, this form of treatment should be immediately instituted.

### SUMMARY

The Rh factor is an antigenic substance found in the red blood cells of 85 per cent of the white population of the United States. Although isoagglutinins against it do not normally exist in those individuals who are Rh-negative they may be produced by the introduction of Rh-positive cells into the circulation either by transfusion or by transmission from the placental vessels during pregnancy.

Intragroup transfusion reactions may occur if Rh-positive blood is used for an individual who has developed anti-Rh agglutinins.

Transmission of anti-Rh agglutinins to the fetus through the placenta may cause a severe hemolytic anemia which is demonstrable at birth or within a few days afterward. This anemia, with its associated findings, is characteristic of erythroblastosis foetalis. The present theory of the etiology of erythroblastosis is as follows: An Rh-negative woman conceives an Rh-positive child by an Rh-positive man. The Rh-positive fetal cells pass through the placenta into the maternal circulation where antibodies against the Rh factor in these cells are produced. These antibodies return through the placenta to the fetus and cause destruction of its blood cells.

All Rh-negative patients should be transfused with Rh-negative blood. It can be assumed, if testing serum is not available, that all patients who have given birth to infants with erythroblastosis are Rh-negative, and consequently, before a transfusion is given to such a patient, careful crossmatching by a special technic should be employed.

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## CLINICS ON OTHER SUBJECTS

### THE TREATMENT OF PNEUMONIA WITH SULFADIAZINE\*

Five Hundred and Thirty Three Patients in Two Seasons

ITALO F. VOLINI M.D. F.A.C.P.,† GERTRUDE ENGBRING M.D.,‡

JOHN R. PEPPER M.D.§ and HILDEGARDE SCHORSCH M.D.¶

THE literature on the use of the sulfonamides accumulates very rapidly. The various experimental and clinical reports on sulfanilamide, sulfapyridine and sulfathiazole have indicated the effectiveness of these preparations, so that these drugs have quickly become available for use in the therapeutic armamentarium. The ideal sulfonamide has not yet been achieved as evidenced by the continuous chemical, experimental and clinical research for new sulfonamides.

Sulfadiazine (2-sulfanilamidopyrimidine,  $C_{10}H_{10}N_4SO_2$ ) one of a large number of heterocyclic derivatives of sulfanilamide and the pyrimidine analogue of sulfapyridine, was synthesized by Roblin and his associates in the Research Laboratories of the American Cyanamid Company.

#### EXPERIMENTAL STUDIES

The studies for absorption, toxicity and chemotherapeutic activity in experimental animals covering a large number of infections and several species of animals were first reported by Feinstein, Williams and associates. These laboratory studies have been surprisingly confirmed in almost all details by the

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From the Department of Medicine, Loyola University School of Medicine and Cook County Hospital.

† Professor and Chairman of the Department of Medicine, Loyola University School of Medicine, Attending Physician, Cook County and Mercy Hospitals.

‡ Associate Clinical Professor of Medicine, Loyola University School of Medicine. Associate Attending Physician in Medicine, Cook County Hospital.

§ Clinical Assistant in Medicine, Loyola University School of Medicine. Resident Pneumonia Service, Cook County Hospital.

¶ Clinical Instructor in Medicine, Loyola University School of Medicine. Resident Pneumonia Service, Cook County Hospital.



observations of various clinical investigators Feinstein and his co-workers showed that the drug is readily absorbed, produces higher average blood levels and has less toxicity after similar dosages than sulfapyridine or sulfathiazole. In addition, they found that sulfadiazine maintains its concentration in the blood at a higher level, and for longer periods with a relatively low acetylation percentage than the latter drugs. The newer drug possessed equal or superior effectiveness against various common pathogenic bacteria in the experimental animals. Sulfadiazine was found highly effective in the treatment of experimental Freidlander bacillus B infection in mice. One most important finding to which they directed attention was the fact that the

TABLE 1

SULFADIAZINE BLOOD LEVELS IN A NORMAL INDIVIDUAL FOLLOWING THE ADMINISTRATION OF 1 GM ORALLY

Time of Specimen	Blood Levels in Milligrams	
	Free	Total
$\frac{1}{2}$ hour	0	0
1 hour	traces	traces
2 hours	2 87	2 87
3 $\frac{1}{2}$ hours	3 6	4 1
4 $\frac{1}{2}$ hours	3 1	3 6
5 $\frac{1}{2}$ hours	3 1	3 6
6 $\frac{1}{2}$ hours	3 0	3 6
24 hours	1 9	2 3
28 hours	1 75	2 12
30 hours	1 65	2 0
72 hours	traces	traces

solubility of acetyl sulfadiazine in urine is much higher than that of the acetyl derivatives of sulfapyridine and sulfathiazole. The results of these studies indicated that sulfadiazine was worthy of an extensive trial in the bacterial infections of man.

Sulfadiazine is one of the most insoluble of all of the medically employed sulfonamide drugs. Nevertheless, it is readily absorbed when administered orally, appearing as rapidly in the blood stream as sulfapyridine and sulfathiazole. The experiment charted in Table 1 confirms the observations of Feinstein and associates, Peterson and associates, Plumer and Ensworth, and Reinhold and his co-workers. Two hours following a single dose of 1 gm of sulfadiazine orally the blood level was 2 87 mg per

100 cc for the free drug, and the same for the total (no acetylation)

The second experiment (Table 2) conducted on a patient with pneumonia, Type XIV, with positive blood culture shows the blood and urine studies for free and acetylated sulfadiazine. Following an initial dosage of 4 gm orally, with 1 gm every four hours until a total dosage of 20 gm was reached in fifty-eight hours of treatment, the temperature reached normal in twenty-six hours.

TABLE 2

SULFADIAZINE BLOOD AND URINE LEVELS AT INTERVALS AFTER INITIAL DOSE BY MOUTH OF 4 GM. FOLLOWED BY 1 GM EVERY FOUR HOURS IN A CASE OF TYPE XIV PNEUMONIA

Time of Specimen	Blood Levels in Milligrams		Urine Levels in Milligrams	
	Free	Total	Free	Total
4 hours	2.25	2.25	traces	traces
9 hours	4.12	4.12		
12 hours	4.3	4.7	53.7	57.7
14 hours	5.6	5.6	84.4	88.8
16 hours	6.25	6.25	78.1	88.1
21 hours	5.9	6.4		
32 hours	6.8	6.8		
35 hours	7.15	7.15		
40 hours	5.7	5.7	78.1	89.3
58 hours	7.4	7.7		

After Discontinuing the Drug

7 hours	5.6	6.1	120.0	125.0
20 hours	2.75	2.75	56.2	56.88
68 hours	traces	traces	15.9	28.3

*Clinical Result.* Rapid lysis with return of temperature to normal in 26 hours. Total dose, 20 gm. in 58 hours.

A third experiment using sodium sulfadiazine intravenously in a normal individual was performed by administering a single dose of 4 gm in the form of a 5 per cent solution in normal saline. The actual estimations are indicated in Table 3, which shows the time periods with corresponding blood and urinary determinations.

Despite the fact that over 50 per cent of the drug was recovered in the first twenty-four-hour period, the drug was found in the blood at a level of 2.8 mg per 100 cc at the end

of forty-eight hours. As others have observed, sulfadiazine is readily absorbed, produces a relatively high blood level which is maintained because of delayed excretion. The percentage of

TABLE 3

SODIUM SULFADIAZINE BLOOD LEVEL DETERMINATIONS AT INTERVALS AFTER A SINGLE INJECTION OF 4 GM INTRAVENOUSLY

Time of Specimen	Blood Levels		Urine Levels	
	Free	Total	Free	Total
Immediate	12 6	13 8		
$\frac{1}{2}$ hour	11 62	12 3		
1 hour	11 2	11 62		
2 hours	10 64	11 2	127 26	140 1
3 hours	8 68	9 5		
4 hours	8 4	9 1	92 4	103 6
8 hours	8 2	9 0	75 6	84 0
12 hours	7 7	8 3		
21 hours			79 8	116 2
24 hours	5 6	5 8	99 4	119 4
48 hours	2 52	2 8	56 0	81 2
72 hours	1 0	1 1		

blood conjugation is low compared to sulfapyridine and sulfathiazole. Acetylation in the urine accounts for about one third of the total drug.

#### CLINICAL STUDIES

Most of our experience has been with the use of sulfadiazine in pneumococcal pneumonia. As a supply of the drug was not continuously available, sulfathiazole and sulfapyridine were necessarily utilized at times during the period under study. While cases treated with the latter drugs may thus be considered as a control series, unfortunately a fair estimate of the efficacy of sulfadiazine as compared with them is not possible for the reason that the latter were used in what we consider to be the milder pneumonia months or seasons, such as late summer and early fall. Comparative reference will be made to sulfathiazole and sulfapyridine treated patients in publications to be subsequently released.

This report deals with 533 patients treated with sulfadiazine at the Cook County Hospital. It comprises two seasons, each of which included the fall, winter and spring months of 1941-1942 and 1942-1943 respectively.

The method of study included routine sputum typing, blood culture, blood counts and urinalysis. Chest films were obtained in approximately 50 per cent of the cases, especially in those in which doubts of any kind arose. These were necessitated particularly in the latter period of the study, in order to aid in conservation of material and technical help. Urinary studies were made daily on a large number of patients to determine the frequency of crystalluria and microscopic and gross hematuria. At present repeated urinalysis is made routinely after the administration of 20 gm. of the drug or upon evidence of renal disturbance.

#### *Dosage and Administration*

The initial dose consisted of 4 gm. of sulfadiazine, and was followed by 1 gm. every four hours until normal temperature had been maintained for twenty-four to forty-eight hours, depending upon the severity of the clinical evidence and findings. A careful survey was made after unsatisfactory clinical response, in which case a total dosage of 30 gm. was attained. The sodium salt of sulfadiazine, 5 gm. intravenously, was employed where oral dosage was not feasible. Repeated parenteral injections were regulated by the blood level determinations, which also guided the oral use of the drug. Blood levels were obtained after twenty-four to thirty-six hours of administration. Repetition of blood determinations was guided by the clinical response, complications of the drug, or the disease and the clinical progress. Blood levels of 10 mg. per 100 cc. were sought where the clinical response was not satisfactory.

Sodium bicarbonate or other alkalinizers of the urine were not employed. The senior author has insisted, from clinical observations, that results have been less satisfactory when alkali is administered with sulfapyridine, sulfathiazole and sulfadiazine than when it is not. Some experimental evidence has recently been produced which indicates much greater blood and urine acetylation where alkalis are used concomitantly. Alkalis promote absorption and heighten the total level of sulfonamide in the blood. It is axiomatic, however, that conjugated sulfonamides are chemotherapeutically inactive and probably produce more toxic effects, although they are usually more soluble in an alkaline medium.

The supportive and symptomatic treatment was concentrated

TABLE 4

GROSS RESULTS IN 533 CASES OF PNEUMONIA TREATED WITH SULFADIAZINE

	No of Cases	Deaths	Mortality, Per Cent	
Pneumococcus type, 1941-1942	150	7	4.7	Bacteremia in 20 per cent, with 20 per cent mortality
Pneumococcus type, 1942-1943	198	19	9.6	Bacteremia in 27 per cent, with 23.7 per cent mortality
Non-typing, 1942-1943	185	22	11.8	
Totals	533	48	9.0	

TABLE 5

RESULTS IN 150 CASES OF TYPE-SPECIFIC PNEUMOCOCCAL PNEUMONIA TREATED WITH SULFADIAZINE, 1941-1942

Pneumonia Type	All Cases			Nonbacteremic			Bacteremic		
	No	Died	Per Cent	No	Died	Per Cent	No	Died	Per Cent
I	40	2	5	29	0	0	11	2	18.1
II	29	2	6.9	24	0	0	5	2	40
III	9	1	11.1	9	1	12	0	0	0
IV	0	0	0	5	0	0	1	0	0
V	5	0	0	5	0	0	0	0	0
VI	2	0	0	1	0	0	1	0	0
VII	25	0	0	20	0	0	5	0	0
VIII	13	0	0	10	0	0	3	0	0
IX	2	1	50	1	0	0	1	1	100
X	1	0	0	1	0	0	0	0	0
XI	4	0	0	3	0	0	1	0	0
XII	1	0	0	1	0	0	0	0	0
XIII	1	0	0	0	0	0	1	0	0
XIV	1	0	0	1	0	0	0	0	0
XV	1	0	0	1	0	0	0	0	0
XVI	2	0	0	2	0	0	0	1	100
XVII	1	1	100	0	0	0	1	0	0
XVIII	1	0	0	1	0	0	0	0	0
XIX	2	0	0	2	0	0	0	0	0
XX	2	0	0	2	0	0	0	0	0
XXI	1	0	0	1	0	0	0	0	0
XXII	1	0	0	1	0	0	0	0	0
XXIII	1	0	0	1	0	0	0	0	0
XXIV	1	0	0	1	0	0	0	0	0
XXV	1	0	0	1	0	0	0	0	0
XXVI	1	0	0	1	0	0	0	0	0
Total	150	7	4.7	120	1	0.8	30	6	20

Incidence of bacteremia, 20 per cent

mainly on maintaining adequate body fluids. A urinary output of from 1200 to 1500 cc was the primary factor responsible for freedom from complications of drug toxicity. Oxygen therapy was used in less than 3 per cent of the cases. The infrequency of use of type-specified antipneumococcus serum is interesting. Of the six patients who received serum in addition to the sulfadiazine, five succumbed. Unquestionably some patients in the series had received sulfonamides prior to their entrance to the hospital. The type of drug, method of administration and total dosage we were unable to determine in most instances. In a few cases in which no response to sulfadiazine was obtained, either sulfathiazole or sulfapyridine was given. Only occasionally did

TABLE 6

RESULTS FROM SULFADIAZINE TREATMENT DURING THE PNEUMONIA SEASON OF 1942-1943

	No. of Cases	Fatal	Mortality Per Cent
Typed cases of pneumococcal pneumonia	198	19	9.6
Failed to type, but many pneumococci present.	37	9	24.3
Failed to type—primary atypical pneumonia	97	4	4.1
Typing not done	51	9	19.6
Total	383	41	10.7

the second drug seem to produce a result after apparent failure of action of the sulfadiazine.

Table 4 summarizes the gross results from sulfadiazine in the treatment of 533 patients with pneumonia.

Table 5 illustrates the evidence as broken down from the total of 150 patients with typed pneumococcus pneumonia treated with sulfadiazine during the season of 1941-1942. The rather unusually favorable results cannot be attributed to a mild season with low virulence pneumococci, because over 70 per cent of cases were found to be the more serious types of infection, with bacteremia in 20 per cent.

Data given in Table 6 covers several important features which call for elaboration. Five patients, all of whom died, had meningitis when treatment was started, and received large amounts of

TABLE 7

RESULTS IN 198 CASES OF TYPE-SPECIFIC PNEUMOCOCCAL PNEUMONIA TREATED WITH SULFADIAZINE, 1942-1943

Pneumonia Type	All Cases			Bacteremic			Nonbacteremic			Blood Culture Not Taken		
	No	Died	Per Cent	No	Died	Per Cent	No	Died	Per Cent	No	Died	Per Cent
I	31	1	3.2	11	1	9	15	0	0	5	0	0
II	12	1	8.3	1	0	0	6	1	16.6	5	0	0
III	20	3	15				9	2	22.2	11	1	9
IV	18	3	16.6	4	1	25	10	1	10	4	1	25
V	14	0		5	0	0	8	0	0	1	0	0
VI	4	0	0	1	0	0	2	0	0	1	0	0
VII	28	5	18	8	4	50	13	1	7.7	7	0	0
VIII	15	0	0				9	0	0	6	0	0
IX	5	0	0				4	0	0	1	0	0
X												
XI	4	0	0				3	0	0	1	0	0
XII	4	0	0	1	0	0	1	0	0	2	0	0
XIII	3	0	0	1	0	0	1	0	0	1	0	0
XIV	7	2	28.5				5	0	0	2	1	50
XV												
XVI	2	2	100	2	2	100						
XVII												
XVIII	2	0	0				1	0	0	1	0	0
XIX	2	0	0				5	0	0	2	0	0
XX	8	1	12.5				1	0	0	3	1	33.3
XXI	1	0	0									
XXII	1	0	0				1	0	0	1	0	0
XXIII												
XXIV	1	0	0				1	0	0			
XXV	4	0	0	2	0	0	2	0	0			
XXVI												
XXVII												
XXVIII												
XXIX												
XXX												
XXXI												
XXXII												
XXXIII												
Total	198	19	9.6	38	9	23.7	102	6	5.87	58	0	0

type-specific serum in addition to adequate sulfadiazine therapy. In eighteen of the forty-one fatal cases, treatment with sulfadiazine was started on the fourth day of the disease. Seventy-six per cent of the patients were over forty years of age, and 75 per cent of the deaths occurred in individuals over forty years of age.

The average dose of sulfadiazine was 35 gm, particularly confined to 244 patients (63.5 per cent) who showed normal temperatures within a maximum of seventy-two hours of beginning treatment with sulfadiazine. Seventy-five patients (20.6 per cent) responded to therapy in twenty-four hours, 122 (31.8 per cent) in the second twenty-four hours, and forty-seven (11.1 per cent) in the full seventy-two hour period. The highest total amount of the drug given was 67 gm over a period of eleven days.

Among the factors affecting the response to sulfadiazine, the most important is the early initiation of therapy. In 113 cases (30 per cent), treatment was instituted within forty-eight hours after onset of the disease. Only five of these were fatal. In 123 cases (32.1 per cent), treatment was delayed between forty-eight to ninety-six hours, and eleven deaths (8.8 per cent) occurred. This delay approximately doubled the mortality. In 117 cases (30.5 per cent) in which treatment was delayed more than ninety-six hours from onset, seventeen deaths (14.5 per cent) occurred.

In the 1942-1943 season, 198 type-specific pneumococcal pneumonias were studied and treated with sulfadiazine (Table 7). The general mortality percentage was twice as high as in the previous season. However, five patients were admitted with meningitis before treatment with sulfadiazine was started and four more succumbed within twelve hours of admission. This correction alone would bring the percentage mortality to 5 per cent in 1942-1943, thus very closely approximating the 1941-1942 results. Type VII pneumonia was almost as frequent as Type I, and showed particular virulence resulting in high mortality. The incidence of bacteremia was greater in the 1942-1943 series.

#### Toxic Effects of Sulfadiazine

The toxic effects ascribable to sulfadiazine are tabulated in Table 8. The more severe manifestations occurred after at least



25 gm and in most instances after 36 gm were administered. All of the severe urinary complications cleared up readily upon withdrawal of the drug and the forcing of fluids. While attention must be directed to the high incidence of crystalluria, mention must be made that urine specimens when allowed to stand for long periods before examination frequently show more crystals than freshly voided specimens.

Toxic effects upon the urinary tract can in large part be obviated by maintaining a high urinary output averaging from 1200 to 1500 cc daily. High blood levels have been a guide to

TABLE 8

TOXIC EFFECTS OF SULFADIAZINE IN 533 CASES

	No	Per Cent
Urinary tract	87	25.6
Crystalluria only	42	11
Hematuria	57	14.8
Microscopic	54	13.9
Gross	3	0.89
Oliguria	1	
Renal colic	1	
Leukopenia 4000 and below	10	2.6
Drug fever	7	2
Rash	1	0.3
Nausea	2	0.6
Psychosis from drug	1	0.3

the danger of urinary complications. Adequate blood levels have been found to average 8 to 10 mg per 100 cc. Very high levels are occasionally obtained on the four-hour dosage method. In the series of cases studied, urinary complications have been infrequent due to relatively small total dosages. Over a longer time period, the ascertainment of the blood levels and the maintenance of high urinary output

#### Complications of Pneumonia under Sulfadiazine Therapy

Two pleural effusions were observed, with no organisms found. Four patients developed empyema while under therapy, an incidence of 1.1 per cent. One fatal case of acute endocarditis was found on postmortem examination. Five patients had meningitis, all dying despite combined serotherapy and chemotherapy. Delayed resolution was encountered in five instances. Otitis media appeared only once.

## CONCLUSIONS

Sulfadiazine is particularly effective in the therapy of pneumonia. It is more active against a greater variety of organisms producing this disease. It is without effect in the primary atypical pneumonia in the majority of cases, although occasional sudden defervescence of fever occurs upon sulfadiazine therapy. Despite the relative insolubility of sulfadiazine in water, oral administration results in rapid absorption with a much higher blood level than is usually obtained from related sulfonamides. This high blood level is more easily sustained on average therapeutic dosage.

The percentage of conjugation in the blood is lower than with the related compounds, usually averaging about 10 per cent.

Excretion through the kidneys is relatively slow, which probably accounts for the sustained high blood level of the drug. The acetyl derivative in the urine constitutes about 30 per cent of the total drug. The most frequently encountered and reported toxic effects are upon the urinary tract.

The complications of pneumonia have been observed much less frequently in the sulfadiazine-treated patient. Sodium sulfadiazine has been used by intravenous injection without dangerous complications. This parenteral route is frequently necessary and has especial effectiveness in producing a high blood level in a short period of time with pronounced therapeutic benefit.

Based on the experience cited, of the sulfonamides sulfadiazine possesses the greatest therapeutic efficiency and the least toxicity in the treatment of pneumococcal pneumonia.

# ERRORS IN THE DIAGNOSIS OF NEOPLASTIC LESIONS OF THE RECTUM, RECTOSIGMOID AND COLON\*

JOSEPH B KIRSNER, M.D., Ph.D.†

and

WALTER LINCOLN PALMER, M.D., Ph.D., F.A.C.P.‡

ALTHOUGH numerous writers<sup>1-8</sup> have emphasized the clinical features and early diagnosis of carcinoma of the colon and rectum, many lesions continue to be overlooked until they are far advanced Rankin<sup>9</sup> found, in a series of 1725 patients with malignant disease of the rectum, that only 55 per cent were suitable for operation and only 35 per cent of the lesions were resectable Swinton and Warren,<sup>10</sup> in a review of 300 patients with carcinoma of the colon and rectum, reported that the average duration of symptoms at the time of operation was nine months The late diagnosis of tumors of the bowel is attributable in many instances to delay by the patient in seeking competent medical attention<sup>11</sup> An even more important cause, according to Rankin, is the failure to make a proper search for the lesion when the patient presents himself with symptoms

The purpose of this paper is to point out the errors in diagnosis committed in seven representative patients in the hope of stimulating, thereby, greater interest in the earlier detection of tumors of the rectum, rectosigmoid and descending colon

## Failure to Examine Rectum in Presence of Classical Symptoms of Carcinoma

CASE I—A S, a forty-year-old housewife, had experienced episodes of lower abdominal cramping pain and diarrhea with the passage of many stools containing blood and mucus for a period of ten months A diagnosis had been made of "colitis" for which the patient had been treated with diets and sulfanilamide without relief

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\* From the Frank Billings Medical Clinic and Department of Medicine, University of Chicago

† Assistant Professor of Medicine, University of Chicago School of Medicine, Attending Physician, Albert Merritt Billings Hospital

‡ Professor of Medicine, University of Chicago School of Medicine, Attending Physician, Albert Merritt Billings Hospital

The physical examination was normal, but the rectal and proctoscopic examinations disclosed a large, firm, fungating mass 7 cm. above the anal ring. The microscopic diagnosis of the lesion was adenocarcinoma of the rectum. A combined abdominoperineal resection was performed, from which the patient made an excellent recovery. Tumor tissue was found in several regional lymph nodes.

*Comment*—Daniel Fisk Jones<sup>12</sup> has remarked "There is no disease that can be diagnosticated with more accuracy than cancer of the rectum after the patient has once presented himself and, yet, there are few diseases which are diagnosticated so late in their course." The late Frank Billings, according to tradition, is authority for the statement that the function of the consulting physician is to make a rectal examination. It is no exaggeration to say that many rectal cancers are overlooked because of failure to examine the rectum. This neglect is all the more striking in this case because of the persistence of classical symptoms for almost one year.

#### Carcinoma of Rectum Overlooked in Presence of Other Pathologic Conditions

CASE II—T R., a seventy-year-old male, had noted difficulty in urination for ten years. Twenty-four years previously he had been ill with "heart disease." There were no symptoms referable to the digestive tract. Physical examination was negative except for obesity. Rectal examination was reported as revealing a grossly enlarged, smooth prostate. The hemoglobin measured 16 gm., the leukocyte count was normal. The urine contained a slight amount of albumin. An electrocardiogram demonstrated left axis deviation and probably a healed posterior infarct. The patient was referred to the Urology Clinic where rectal examination disclosed, in addition to the enlarged prostate, an irregular mass arising from the anterior wall of the rectum 5 cm. above the anal ring. Further rectal and proctoscopic examinations confirmed the presence of the tumor. The microscopic diagnosis was adenocarcinoma.

CASE III—J T R., a fifty-four-year-old minister, had experienced itching and burning of the anal region for fifteen months. Rectal examination was described as very painful and apparently never had been thoroughly performed. A diagnosis of fistula in ano had been made for which the patient was treated with local cauterization, the application of gentian violet, and suppositories. The fistula failed to heal. Further inquiry revealed that in the preceding twelve months the patient had experienced numerous episodes of constipa-

tion and diarrhea. For five months prior to admission he had noted an increasing urge to defecate, frequently without result. In addition, a considerable quantity of fresh blood had been passed per rectum six weeks previously. Physical examination revealed an enlarged liver. Rectal examination disclosed a fistula in ano and also a probable mass high in the rectum. Proctoscopy demonstrated a large, nodular, ulcerated, bleeding mass on the anterolateral wall of the rectum 8 cm above the anal ring. The microscopic appearance of the lesion was strongly suggestive of carcinoma. A combined abdominoperineal resection was performed from which the patient made a satisfactory postoperative recovery. Microscopic examination revealed the tumor as an adenocarcinoma which had penetrated the entire width of the bowel wall and had extended to the regional lymph nodes.

*Comment*—The value of a careful, routine digital examination of the rectum in the diagnosis of rectal cancer cannot be over-emphasized. Certainly there are few procedures which will elicit such valuable information with the expenditure of so little effort, yet there is probably no examination that is more consistently neglected. All cancers of the rectum and at least 75 per cent of all lesions of the rectosigmoid are within reach of the examining finger, the remaining tumors of the rectosigmoid may be visualized through the proctoscope. The attending physician in each case apparently had been misled by the presence of other pathologic conditions (enlarged prostate, fistula in ano). It is of interest to note in this connection that, in 10 per cent of Rankin's series of patients with carcinoma of the rectum, operations for hemorrhoids had been performed elsewhere after the onset of the symptoms of malignant disease.<sup>13</sup> Case II is noteworthy because of the complete absence of symptoms referable to the carcinoma. Similar cases have been encountered by others.<sup>14</sup> In Case III the original physician had also failed to elicit symptoms which are commonly associated with carcinoma of the rectum.

#### Importance of Routine Proctoscopic Examination in Diagnosis of Carcinoma of Rectosigmoid

CASE IV—P W, a fifty-seven-year-old fireman, sought medical attention to determine whether or not he had diabetes. He had lost 33 pounds in weight in six months. Physical examination was normal except for irregular pupils which reacted sluggishly to light. Rectal

examination was negative. The blood count was normal. One of several urine specimens contained reducing substances. The Wassermann and Kahn reactions were negative. The stools gave slightly positive reactions for occult blood. Roentgen study of the esophagus, stomach, duodenum, colon and terminal ileum was reported as normal. The patient was given a measured diet adequate in calories, but during the next two months he lost an additional 15 pounds. The continued loss of weight suggested the presence of a neoplasm, and the patient was referred to the gastro-intestinal clinic for further study. Proctoscopy revealed a mushroom-like growth, about 2 cm in diameter situated on the posterior wall of the bowel 12 cm above the anal ring. The microscopic diagnosis of biopsies taken from the lesion was adenocarcinoma. The tumor was removed by a local resection of the rectosigmoid. The patient made an excellent postoperative recovery.

**CASE V—M T.**, a thirty-eight-year old salesman, had experienced burning pain in the rectum for one year prior to admission. The pain had been relieved by the use of suppositories prescribed by a local physician. Fresh blood had been noted in the stools for three months. The bowel movements usually were well formed, but there had recently been an episode of diarrhea lasting several days. Physical examination was normal. Rectal examination revealed only the presence of internal hemorrhoids. The blood count and urine analysis were normal. Examination of a warm stool was negative for parasites. Three stools, obtained during the use of a meat-free diet, gave strongly positive reactions for occult blood. Proctoscopy demonstrated a polypoid, friable, bleeding mass encircling the bowel 12 cm above the anal ring. The microscopic diagnosis was adenocarcinoma. Roentgen examination failed to demonstrate the lesion seen through the proctoscope.

**Comment**—Both cases illustrate the importance of a routine proctoscopic examination in the diagnosis of carcinoma of the rectosigmoid. Case IV is of interest in that the only clue to the presence of a neoplasm was continued loss of weight. Case V emphasizes the need for investigation of all rectal symptoms no matter how unimportant they may appear to be. Had this been done one year previously when suppositories were prescribed for rectal pain, it is likely that the carcinoma would have been detected at a stage more favorable for "surgical cure." The failure of the radiologist to demonstrate the carcinoma is not surprising, for the unreliability of the roentgenologic method in

the diagnosis of lesions of the rectum and rectosigmoid is well known

### Failure of Roentgen Examination and the First Two Proctoscopies to Demonstrate Carcinoma of Rectosigmoid

CASE VI—L F B, a sixty-one-year-old unemployed male, had noted lower abdominal cramping pain and the presence of blood and mucus in the stools for eight months. He had lost 9 pounds in weight in one week. Physical examination, including digital examination of the rectum, was normal. The blood count and urine analysis were normal. The maximum free hydrochloric acid after the injection of histamine (0.81 mg) was 45 clinical units. Examination of a warm stool was negative for parasites. Stools, obtained during the use of a meat-free diet, contained occult blood. Gastroscopy revealed a normal gastric mucosa. Proctoscopy for a distance of 20 cm was reported as negative. Roentgen examination of the esophagus, stomach, duodenum, colon and terminal ileum was reported as normal. The patient was treated by the use of a bland diet, sedatives, antispasmodics and vitamins. His symptoms persisted, however, and occult blood was consistently demonstrated in the stools. A second proctoscopic examination for a distance of 18 cm was reported negative. The treatment was continued, but inasmuch as the patient's symptoms increased in severity, he was referred to the Gastro-intestinal Clinic, eight months after his initial visit and sixteen months after the onset of illness. Proctoscopy at this time revealed an irregular polypoid mass on the posterolateral wall of the rectosigmoid, 14 cm above the anal ring. Because of the severe pain induced by the procedure and to make more certain of the diagnosis, the examination was repeated with the patient anesthetized by nitrous oxide. The presence of a tumor mass at the rectosigmoid was confirmed, the microscopic diagnosis was papillary adenocarcinoma of the rectosigmoid. Roentgen study of the colon again failed to demonstrate the lesion. A modified Mikulicz operation was performed with removal of the lower sigmoid colon. The patient made an uneventful postoperative recovery. Tumor tissue was found in several regional lymph nodes.

*Comment*—Two factors contributed to the late diagnosis in this case, namely (1) the patient's delay in seeking medical attention and (2) the failure of the roentgen examination and the first two proctoscopies to demonstrate the carcinoma. It should be noted to the credit of the attending physician, however, that he was sufficiently impressed by the persistent symp-

toms and the continued presence of occult blood in the stools to pursue the search for organic disease. Persistence of symptoms suggestive of carcinoma of the rectum or sigmoid, following negative proctoscopic and roentgenologic studies, not infrequently signifies that the examinations have been inadequate. If, on repeated rectal examinations, the cause of such symptoms is not found, or in the event the procedures have been unsatisfactory, it is advisable to have the patient examined by a physician trained in proctoscopic methods. It is difficult to understand how the proctoscopist, even though relatively inexperienced, could have passed the proctoscope 20 cm on the first examination and 18 cm on the second without encountering the tumor found later 14 cm from the anus. Nevertheless, this was the case, it is not a unique experience for on several occasions growths have been demonstrated by experienced examiners in patients said to have been proctoscoped previously with negative findings.

CASE VII—V C., a twenty-seven-year-old housewife had complained of intermittent lower abdominal cramping pain and flatulence for five years. The stools were soft and occasionally contained fresh blood. There had been no weight loss. The patient had consulted many physicians and had undergone many treatments including the removal of her appendix, without relief of symptoms. Physical examination was normal except for slight pallor of the skin. The Wassermann and Kahn reactions were negative. The maximum free hydrochloric acid injection of histamine (0.51 mg) was 87 clinical units. The red blood cell count was 3,490,000, the hemoglobin measure 95 gm, the leukocyte count was normal. Stools obtained during the use of a meat-free diet gave strongly positive reactions for occult blood by the benzidine test. Roentgen examination of the esophagus, stomach, duodenum, colon and terminal ileum was reported as normal. Proctoscopy disclosed two small polyps on the anterior wall of the rectum approximately 10 cm above the anal ring. Microscopic examinations of the polyps did not reveal any definite evidence of malignant change. Treatment consisted in the use of a bland diet, sedatives and antispasmodics. Two additional proctoscopic examinations within the next ten weeks were normal. The patient seemed to improve slightly, but because of a persistent secondary anemia and the continued presence of occult blood in the stools, she was hospitalized for further study. A second roentgen examination now revealed a polypoid tumor in the midportion of the descending colon. T



well shown in Figure 37 The patient underwent a resection of the sigmoid and descending colon from which she made an excellent postoperative recovery The surgical specimen contained many small up to 5-mm polyps projecting from the mucosa In addition, there were three large polypoid masses each attached to the mucosa

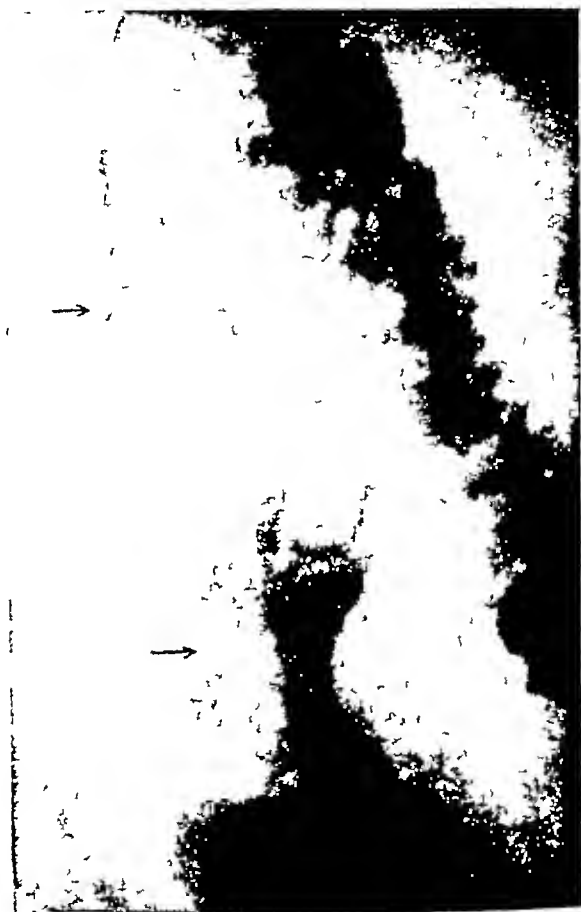


Fig 37 (Case VII) —Polypoid tumor of descending colon demonstrated at second roentgen examination

by long stalks No evidence of carcinomatous change was detected on microscopic examination.

*Comment* —This case illustrates the importance of continuing the search for organic disease of the bowel in individuals with a persistent secondary anemia and persistent loss of blood in the stools Useless and potentially dangerous treatment had been attempted for five years because of insufficient regard for these

important laboratory findings. This case demonstrates also that a single reportedly normal roentgenologic examination is not sufficient evidence to rule out organic disease if the clinical course and laboratory studies indicate otherwise.

#### SUMMARY AND CONCLUSIONS

The seven case reports presented re-emphasize the fact that the early diagnosis of carcinoma of the colon and rectum depends upon a thorough investigation of all symptoms regardless of how trivial they may appear. This investigation must include

- 1 A detailed history of the patient's illness
- 2 A complete physical examination
- 3 *Digital examination of the rectum*
- 4 *An adequate proctosigmoidoscopic examination*
- 5 Careful roentgenologic study of the colon
- 6 A routine blood count
- 7 A routine analysis of the stools for occult blood

In the presence of persistent symptoms, secondary anemia, or occult blood in the stools, the search for organic disease must be continued until the cause of the symptoms and the source of the bleeding are discovered.

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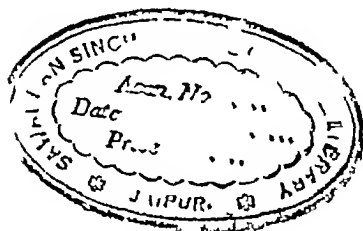
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## CONTRIBUTORS TO THIS NUMBER

John B Andosca, M.D, F C C P, Chief Resident Physician, Boston Sanatorium, Instructor in Medicine, Boston University School of Medicine, Boston

Alvan L. Barach, M D, F A C P, Associate Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University, Assistant Attending Physician, Presbyterian Hospital, New York City

George E Burch, M D, F A C. P, Associate Professor of Internal Medicine, Tulane University School of Medicine, Visiting Physician, Charity Hospital in New Orleans and Touro Infirmary, Consultant in Cardiovascular Diseases, Ochsner Clinic, New Orleans

Russell L. Cecil, M D, Professor of Clinical Medicine, Cornell University Medical College, Attending Physician, New York Hospital, Visiting Physician, Bellevue Hospital, New York City

Thomas Findley, M D, F A C P, Assistant Professor of Clinical Medicine, Tulane University School of Medicine, Director of Section on Internal Medicine, Ochsner Clinic, and Visiting Physician, Touro Infirmary, New Orleans

John A Foley, M D, F A C P, Chief-of-Staff, Boston Sanatorium, Clinical Professor of Medicine, Boston University School of Medicine, Director, Fifth and Sixth Medical Services, Boston City Hospital, Boston

Clyde A Heatly, M.D, F A C S, Associate Professor of Surgery, in Charge of Otolaryngology and Bronchoscopy, University of Rochester, School of Medicine and Dentistry, Otolaryngologist-in-Chief, Rochester Municipal and Strong Memorial Hospitals, Rochester, New York

Chevalier Jackson, M D, F A C S, Honorary Professor of Broncho-Esophagology and Consultant in Research, Broncho-Esophagologic Research Laboratories, Temple University Medical School, Philadelphia

Chevalier L. Jackson, M D, F A C S, Professor of Broncho-Esophagology and Director of Broncho-Esophagologic Research Laboratories, Temple University Medical School, Philadelphia

# CONTRIBUTORS TO THIS NUMBER

Foster Kennedy M D , F.R.S (Edin ), Professor of Neurology, Cornell University Medical College, Director Neurological Department, Bellevue Hospital, New York City

Robert F Loeb, M D , F.A C P , Lambert Professor of Medicine, College of Physicians and Surgeons Columbia University, Associate Attending Physician Presbyterian Hospital and Neurological Institute, New York City

Walsh McDermott, M D Assistant Attending Physician New York Hospital, Instructor in Medicine, Cornell University Medical College, New York City

T Grier Miller M D F A C P Professor of Clinical Medicine, School of Medicine, University of Pennsylvania Chief of Gastro-Intestinal Section (Kinsey-Thomas Foundation) of Medical Clinic, University of Pennsylvania Hospital Philadelphia

Walter Lincoln Palmer, M D , Ph D , F A C P Professor of Medicine, School of Medicine, University of Chicago, Attending Physician, Albert Merritt Billings Hospital, Chicago

P S Pelouze M D , Assistant Professor of Urology, School of Medicine University of Pennsylvania, Special Consultant, U S Public Health Service, Philadelphia

Howard F Polley M D Consultant in the Division of Medicine, Mayo Clinic, Rochester, Minnesota.

Paul Reznikoff, M D , Associate Professor of Clinical Medicine, Cornell University Medical College Attending Physician, New York Hospital Visiting Physician, Bellevue Hospital, New York City

William T Salter, M D , F A C P Visiting Lecturer from Yale University, School of Medicine, Department of Pharmacology, University of California Medical School and the Thyroid Clinic, University of California Hospital, San Francisco

Donald J Simons, M D Assistant Professor of Clinical Medicine (Neurology), Cornell University Medical College Physician to Out-patients, New York Hospital, Attending Neurologist Midtown Hospital, New York City

Charles H Slocumb, M D., Assistant Professor of Medicine Mayo Foundation University of Minnesota, Consultant in Division of Medicine, Mayo Clinic, Rochester, Minnesota

Mayo H Soley, M D , Associate Professor of Medicine, University of California Medical School, Associate Visiting Physician Consulting Pharmacologist, University of California Hospital Visiting Physician, San Francisco Hospital, San Francisco

Copy 4

## CONTRIBUTORS TO THIS NUMBER

Eugene A. Stead, Jr., M D , Professor of Medicine and Chairman of the Department, Emory University School of Medicine, Visiting Physician, Grady Hospital, Atlanta, Georgia

Willard O. Thompson, M D , F A C P , Professor of Medicine (Rush), University of Illinois College of Medicine, Associate Attending Physician, Presbyterian Hospital, Chicago

James V. Warren, M D , Instructor in Medicine, Emory University School of Medicine, Visiting Physician, Grady Hospital, Atlanta, Georgia

Julius L. Wilson, M D , F A C P , Associate Professor of Medicine, Tulane University School of Medicine, Visiting Physician, Charity Hospital in New Orleans, Associate in Internal Medicine, Ochsner Clinic, New Orleans

Harold G. Wolff, M D , F A C P , Associate Professor of Medicine (Neurology), Cornell University Medical College, Associate Attending Physician, New York Hospital, Assistant Attending Psychiatrist, Payne Whitney Psychiatric Clinic, New York City

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# THE MEDICAL CLINICS of NORTH AMERICA

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## SYMPOSIUM ON CHRONIC DISEASES

### INTRODUCTION

IN recent years the medical profession has become more and more aware of the importance of chronic disease, not only with respect to curative measures for the individual patient, but from the broader standpoint of public health as well. We are very apt to think of chronic disease as synonymous with old age, but the studies by Mary C. Jarrett on 'Chronic Illness in New York City' show that nearly half of all the chronically ill persons in this census were under forty years of age. About one third were children under sixteen, chiefly children with orthopedic disorders.

Chronic disease is by no means confined to the disorders of wear and tear. Many of the infections, notably syphilis and tuberculosis, fall in the category of chronic disease, and many of the disturbances of somatic physiology and chemistry also run a chronic course. Thanks to modern medical research, we are learning that many chronic diseases which were formerly considered incurable respond well to rational therapy. The achievements of modern orthopedic surgery put many cripples on their feet again and the new accelerated treatment of syphilis promises to take this infection entirely out of the chronic disease group. The prognosis for pulmonary tuberculosis has improved greatly in recent years, while gold therapy brings renewed hope to many patients with rheumatoid arthritis. Even in diseases of the nervous system the picture has brightened: shock therapy in its various forms offers a very promising field for further investigation.

In her study 'Chronic Illness in New York City' Miss Jarrett points out that chronic disease is always a medical social problem and that chronic patients are in particular need of social service. They are also in need of much better institutional care than they now receive. The writer hopes that after the war one of the results of the present agitation over improved medical care will be better hospital facilities for the chronically ill. The Goldwater Memorial Hospital

only recently built for the chronically ill of New York City, provides an excellent model which might well be followed by other American cities. In the field of chronic arthritis, the most prevalent of all chronic ailments, the present facilities for institutional care are shockingly poor. It is almost impossible to provide first-class institutional care for the arthritic patient unless he has unlimited means, and even then the problem is none too easy.

Studies such as those included in this volume of *Medical Clinics* give the reader a vivid idea of the immensity of the chronic disease problem. They also serve to inspire the practitioner with renewed interest and enthusiasm in the therapy of chronic illness.

RUSSELL L. CECIL

## RECENT ADVANCES IN THE TREATMENT OF SYPHILIS

WALSH McDERMOTT, M.D.\*

IN the past few years a number of innovations have been made in the treatment of syphilis. Evaluation of any method of antisyphilitic therapy requires months or years, because of the long course of the infection. When such innovations are following one another in rapid succession, as they are at present, only tentative appraisals of their worth are attainable.

As the early (i.e., infectious) syphilitic infections present a clinical entity uncomplicated by permanent damage to vital structures, and one in which changes in the status of the infection can most readily be determined by our present methods, it is natural that most of the recent changes in the field of syphilotherapy should be studied in patients in this stage of the disease. Knowledge obtained from the study of the effects of the new methods on early syphilitic infections is being more slowly adapted and applied to both latent and symptomatic forms of the later disease.

Outstanding innovations in the therapy of early syphilis have been the introduction of intensive arsenotherapy by Hyman, Chargin, Leifer and their collaborators,<sup>1</sup> the exhaustive animal experiments of Eagle and Hogan,<sup>2</sup> the use of fever as an adjunct to arsenotherapy by Simpson, Rose and Kendell,<sup>3</sup> and by Thomas,<sup>4</sup> and the recent pilot experiment reported by Mahoney of the use of penicillin on four patients with primary syphilis.<sup>5</sup> In addition, the reawakening of interest in the use of bismuth as a part of various systems of intensive therapy is worthy of note.<sup>6</sup>

### INTENSIVE ARSENOTHERAPY OF EARLY SYPHILIS

Methods of intensive arsenotherapy in early syphilis fall into three general categories: (1) the five-day drip, (2) combinations of fever and arsenotherapy by syringe for relatively short periods of one or two weeks, and (3) biweekly or triweekly injections of arsenoxide for longer periods (six weeks to six months) combined with short courses of bismuth.

**The Five Day Drip.**—It is important to emphasize that the real impetus behind all of these intensive systems was supplied by the demonstration by Hyman, Chargin and Leifer<sup>1</sup> that it was possible to cure the majority of a large series of patients with early syphilis in the short period of five days. Following the study of a small series of patients

\* Assistant Attending Physician, New York Hospital; Instructor in Medicine, Cornell University Medical College, New York City.



treated by this method in 1935, these workers and their collaborators set up in 1938 a large scale study of the system. Male patients with early syphilis were admitted to the Mt Sinai Hospital, where they received large amounts of trivalent arsenical administered by intravenous drip over a period of five consecutive days. On discharge from the hospital, alternate patients reported to the Bellevue clinic and to the clinic of the New York Hospital for all subsequent follow-up study. We have had the opportunity of following approximately one half of these patients, starting from the time immediately after their therapy had been concluded.

*Dosages, Therapeutic Efficacy*—A first group of slightly over 100 patients, of whom forty-seven reported to us, were treated with 4.2 gm of neoarsphenamine during the five-day period. As this series was growing, none of the common serious reactions to the arsenic were observed, with the exception of peripheral neuritis, which occurred in 35 per cent of the patients. This complication, as seen in our part of the series, was extremely mild and in itself would not have constituted any serious drawback to the treatment. However, after 109 patients had been treated with favorable therapeutic response and with no untoward happenings, two patients developed toxic encephalopathy, which, in one, proved fatal. Accordingly, the use of neoarsphenamine was discontinued and mapharsen was substituted. Because of this unhappy experience, the Mt Sinai group quite properly became ultra-conservative in the initial dose of mapharsen and the rate at which subsequent dosage was increased. The dose finally attained, and the one recommended by the originators of the treatment, is 1200 mg of mapharsen, or roughly the equivalent of twenty weeks' treatment on the standard regimens.

In the group treated during the preliminary period with a dosage ranging from 0.5 to 1.0 gm of mapharsen, the therapeutic results were only fair (fifteen out of seventy-six were failures in our half of the series). However, no attempt should be made to examine these figures too critically from the standpoint of therapeutic efficacy. In the first place, eleven of the fifteen reported failures were in patients who developed infectious syphilis subsequent to their originally treated infection. In all probability, a few of these, at least, represent reinfections. Of more importance is the fact that all of the members of this group were treated with a total dose which is considered to be inadequate by the originators of the treatment. Yet despite this, the majority achieved good initial therapeutic results. There was no apparent correlation between the dosage and the treatment failures, some patients attained good results with one half of a dose which failed to work in some others. This immediately suggests that, if the effects of intensive treatments are studied from the standpoint of such factors as body weight, possible differences in excretion of the drug and the

like, individualization of the total dosage might be associated with better results

Of fifty-five patients in the group treated with 12 gm of mapharsen, thirty-five were followed for one year after cessation of the treatment. Twenty-nine were classified as apparently well, and six as failures, including four classified as relapse or reinfection. After two years, no new failures had appeared, but a large number of patients had disappeared, so that all we can show as known two-year results from the fifty-five patients originally seen by us are seventeen patients apparently well, and the six failures. It is, of course, extremely probable that the majority of the fifty-five who have disappeared have achieved satisfactory results.

*Relapse or Reinfection*—Four of the six patients labeled as failures in the group treated with 12 gm of mapharsen, eleven in the group treated with 0.5 to 1 gram of mapharsen, and three in the group treated with neoarsphenamine—a total of eighteen patients—developed infectious syphilis subsequent to the treatment for the first attack of infectious syphilis. These eighteen patients are actually classified as having "relapse or reinfection." It is unfortunate that they cannot be classified more exactly as it obviously makes a great difference in the interpretation of the results as to under which heading they belong. In some instances of recurrent infectious syphilis, one may feel reasonably sure that the patient is having a relapse and not a reinfection or vice versa, but, since these second infections occur at such a short interval after the original infection, as within one or two years it is actually impossible to decide with any degree of accuracy. It is our opinion that the great majority of these cases represent relapses, but this cannot be established one way or the other.

It is of interest to compare the incidence of such second attacks of infectious syphilis in this intensively treated group with that occurring in patients treated by the standard method. In a consecutive series of 102 of our patients with infectious syphilis, who had completed the standard eighteen months' treatment and who have been followed for from one to five years thereafter only two have subsequently developed infectious syphilis, whereas in the series of 163 treated intensively at Mt Sinai Hospital and followed by us there were 18 such cases. The patients in both groups were in the same social and economic level, most of them having been referred from the same agency, so that there is no reason to believe that sexual promiscuity was more prevalent in one than the other. It is entirely possible, as has recently been suggested by Schoch<sup>7</sup> that when an early syphilitic infection is treated by the longer methods, some resistance to a fresh inoculation develops despite the apparent biologic cure so that these intensively treated syphilitics may actually be more susceptible to reinfection than the members of the group treated by the longer system.

Including all second bouts of infectious syphilis under the heading of failures, Leifer, Chargin and Hyman<sup>8</sup> reported satisfactory results in 83 per cent of their patients treated with 1200 mg of mapharsen. This approximates the results obtained by the eighteen months' system of the Cooperative Clinic Group.<sup>9</sup> Although the two series are not strictly comparable, it appears that 1200 mg given in five days by intravenous drip is quite as effective as the longer treatment.

*Relative Frequency of Toxic Encephalopathy*—Most of the complications of arsenical therapy such as dermatitis, hepatitis and involvement of the bone marrow were encountered infrequently during intensive treatment with mapharsen. The rarity of such reactions is not surprising, since their incidence following the use of mapharsen has not been high in the prolonged systems of treatment and in general has not depended upon the size of the dose. In contrast to this, the incidence of toxic encephalopathy with any system of arsenotherapy seems to bear a direct relationship to dosage. This much dreaded concomitant of arsenic therapy has been characterized clinically by the relatively sudden development during treatment of mental confusion and convulsive phenomena.

In both the neoarsphenamine and the mapharsen series, the incidence of this type of arsenical reaction has been alarmingly high. It is difficult to estimate the exact incidence of encephalopathy among patients treated by standard methods. Certainly its occurrence has been extremely rare. At the New York Hospital it has not been encountered during a seven-year period in which 4600 patients received 56,480 doses of trivalent arsenicals, including both arsphenamines and arsenoxides. In Moore's clinic at Johns Hopkins, it was seen only twice among 45,000 patients treated by conventional methods.<sup>10</sup> In the United States Navy, where facilities for follow-up are excellent, toxic encephalopathy was encountered only once following 1,000,000 injections of neoarsphenamine.<sup>10</sup> These figures must be compared with an incidence of 1.8 per cent of toxic encephalopathy in the neoarsphenamine series and 1.1 per cent in the mapharsen group of the original five-day drip experiment at Mt. Sinai Hospital,<sup>8</sup> and with the incidence of approximately 1 per cent in a much larger collected series of patients treated by this method. In 1600 patients treated with the five-day drip, there was a fatality rate from toxic encephalopathy of 0.3 per cent, or roughly one in 300 patients treated.<sup>11</sup>

It should be emphasized that the high incidence of this serious type of reaction is not unique to the intravenous drip therapy, but occurs to the same extent among patients treated by any of the intensive treatments which require only one or two weeks for completion. Deaths due to the treatment of early syphilis are particularly distressing because of the fact that syphilis in the infectious stage is practically always fatal. To be sure, fatal reactions other than toxic enceph-

alopathy will occur in the arsenical treatment of syphilis by whatever system is employed, but, since the development of these other reactions bears no direct relationship to the dose of drug used, and occurs much less frequently when the arsenoxide preparations are used, it is probable that deaths from these sources would be equally few under prolonged or intensive regimens.

*Present Status of Method*—The crux of the situation in regard to the overall value of the five-day drip and other systems for intensive arsenotherapy of early syphilis lies in the demonstration that by these methods it is possible to achieve therapeutic results at least the equal of those attainable by the prolonged systems in a period of only a few days or weeks, but at a much higher cost in terms of toxic reactions of the nervous system. As it stands now, the five-day drip method has not proved itself to be a satisfactory method for the treatment of syphilis, but the information gained from this clinical experiment of Leifer, Chargin and Hyman has led the way to a drastic shortening of the period of time necessary for the proper treatment of early syphilis.

*Combinations of Fever and Arsenotherapy for One or Two Weeks.*—Modifications of the original five-day drip technic have been carried out by numerous investigators in efforts both to make the method less complex and to reduce the incidence of encephalopathy. Thomas<sup>12</sup> concluded on the basis of an extensive experience that, when 1200 mg of mapharsen were given by syringe over time periods comparable to the drip regimen, the incidence of encephalopathy was slightly higher. Although this incidence could be appreciably lowered by using less mapharsen (under 1000 mg total dose) during the same time period, the rate of relapse of the syphilis rose correspondingly, exactly as had been noted with comparable low doses by drip technic. By introducing *typhoid vaccine induced fever* into the scheme he sought to achieve the good therapeutic results of the high mapharsen dosage while staying within the safer range of the lower doses. In his first series of 549 such combined treatments, toxic encephalopathy developed seven times (1.28 per cent). The therapeutic results were quite comparable to those obtained by the other prolonged and intensive systems. However, by reducing the mapharsen dosage to below 800 mg over ten days combined with three or four bouts of fever, he has treated over 800 patients since July, 1942, without encountering a single instance of toxic encephalopathy and with no apparent sacrifice of therapeutic efficacy.<sup>13</sup>

For some years Simpson, Kendall and Rose<sup>3</sup> have been investigating various combinations of arsenic and *mechanically induced fever*, and in 1942 reported good preliminary results in a small series of patients treated by various combinations of these two agents. We have had no direct experience in the use of these combinations of fever and

chemotherapy Fever therapy, regardless of the method used, is not without its dangers,<sup>1</sup> entirely apart from the dangers of the associated chemotherapy<sup>14, 15</sup> Whereas fever is the ideal method for the treatment of some forms of neurosyphilis, where the immediate threat of the disease far outweighs any such dangers from treatment, such a situation does not exist in the early syphilitic infections

**Biweekly and Triweekly Systems of Intensive Arsenotherapy**—Eagle and Hogan<sup>2</sup> in a series of painstaking and exhaustive experiments, have supplied the fundamental knowledge necessary to solve this challenging problem of how to obtain the beneficial results of the intensive systems without so much attendant risk These workers have thoroughly investigated the time-dose relationship of a number of different experimental systems for the treatment of syphilis in rabbits, ranging in duration from ten seconds to six weeks They found that within these time limits the total amount of mapharsen necessary to cure syphilis in rabbits varied very little If a total dose within certain limits was used, there was surprisingly little difference from a standpoint of therapeutic efficacy whether it was administered over a period of a few hours, a few days, or a few weeks, or whether it was given by continuous drip or multiple syringe injections They point out, from a study of the published data, that the same phenomenon seems to hold true for infectious syphilis in man, i e., that it takes somewhere around 1200 mg of mapharsen to effect apparent cure whether the dose is given by intravenous drip in five days or by multiple injection over a few weeks

Yet, despite the remarkable uniformity of the total dose necessary for cure regardless of how, or (within limits) how long, it was administered, they found that the margin of safety in terms of animal toxicity was very definitely increased in the longer systems and narrowed in the shorter ones Using an essentially constant total curative dose, they were able to predict quite accurately the incidence of serious toxicity which would occur in their animals on a system of any given duration Thus, they have been able to calculate the factor of safety of a treatment of any duration in rabbits, and, applying their calculations to intensive treatments in man, have been able to show that it would have been possible to predict quite accurately the incidence of serious toxicity which has actually been observed with the various intensive systems

Once this fundamental information was obtained, the problem was simply to choose a period of time which would best satisfy the twin demands of speed and safety for the administration of the total dose in the treatment of syphilis in man Eagle and Hogan did not feel that any treatment schedule using mapharsen, which was completed in as short a period as ten or twenty days, provided a reasonable freedom from serious toxic reactions and deaths

Accordingly, in October, 1941, they set up a large scale clinical study of a number of systems of triweekly injections of mapharsen over total periods ranging from six to twelve weeks, some of which were supplemented by bismuth. In addition also on a basis of this work, a treatment system including biweekly injections of mapharsen given over two ten-week periods separated by five weekly injections of bismuth, was adopted by the United States Army Medical Corps.<sup>16</sup> In this latter system, five additional injections of bismuth are given concurrently with each mapharsen course, the over-all duration of treatment being six months.

Study of these various "Eagle systems" is being carried out by a group of some eighty cooperating clinics. During the past fifteen months, fifty-seven patients have been treated at this hospital with the *six-week system*. This consists of triweekly injections of an arsenic oxide derivative (in this series, clorarseo), 40 to 80 mg. per injection depending on weight accompanied by weekly injections of 0.2 gm. of bismuth subsalicylate, over a total period of six weeks. Not all of the systems under trial included the supplementary bismuth. There is evidence that, when administered with arsenic, the toxic effects of the bismuth are not additive, whereas the therapeutic activity is additive to the arsenical.<sup>6</sup> Since the preliminary results indicated that the therapeutic results with triweekly systems were superior when bismuth was given concurrently, Eagle and Hogan now advise its use in all such systems under study.<sup>17</sup>

Our experience with this six-week system has been too limited, in that our series is small and our total period of study short to justify definite conclusions. However, a valid appraisal of the method will be available soon, when the report on over 2500 patients treated by these systems is published by the originators. In our own small experience with it it can be said that the immediate therapeutic results are quite comparable to those obtained by the other effective methods and that thus far we have not encountered any of the serious toxic reactions.

Reports on the therapeutic efficacy and incidence of toxicity of the *six-month system* used by the Army are not available at this time, but it would seem from the experience with the other systems and from predictions calculated from Eagle and Hogan's data that it would be a most reasonably safe and effective system.

**Completeness and Permanency of "Cure" by Intensive Methods**—Two questions confront the internist who is attempting to evaluate these rapid treatments of early syphilis. First, how long will it be before we can be reasonably sure that these "cures" obtained so quickly can really be considered to be permanent cures. Second, what factors should be taken into consideration in advising a patient with early syphilis as to which of the many systems of therapy should be used?

In answer to the first question The three main threats which hang over an individual infected by syphilis are (1) the possibility of transmission to others, which in a woman includes the offspring, (2) the possibility of developing syphilis of the aorta with resulting formation of aneurysm or involvement of coronary ostia or aortic valves, (3) the possibility of developing neurosyphilis (Other possibilities exist, but are purposely excluded from discussion because of their infrequency)

In regard to the threat of *transmission to others*, when infectious relapse occurs following inadequate treatment for early syphilis, it usually does so relatively soon after treatment has been stopped In Thomas<sup>14</sup> series, the great majority of such relapses appeared within a six-month period, and in Padget's study of the material from Moore's clinic it was found that 84 per cent of such relapses occur within the first two years of the infection, at an average period of nine months following the cessation of therapy<sup>18</sup> Relapse can occur any time during the first few years, but its appearance after four or five years following the discontinuance of therapy is practically unheard of

As far as the development of *cardiovascular syphilis* is concerned, the available evidence at present points to the conclusion that amounts of arsenical therapy which are grossly inadequate for the complete cure of the infection when given on a weekly regimen are actually sufficient to prevent the development of aortic involvement, provided that this weekly arsenical therapy is given continuously during the early stages of the disease<sup>19, 20</sup> Since, in virtually all of the intensive systems which have been introduced, as much or more arsenic is used as was found to be effective for the prophylaxis of aortic syphilis when given in weekly systems, it would seem that patients treated by the quicker treatments run little or no risk from this threat

When experimental study of the five-day drip was first started, it was feared that there would be a rather high incidence of acute meningal syphilis occurring as a relapse at some time after the treatment Such fears were not borne out by the results, as the incidence of early *neurosyphilis* under the intensive systems has been, in general, quite as low as with the standard technics The possibility of these intensively treated patients developing neurosyphilis ten or twenty years later would seem highly unlikely on the basis of the long experience with the prolonged systems of treatment for early syphilis In general, neurorecurrences appear fairly soon after the cessation of therapy (two or three months),<sup>21</sup> so that, if a patient shows no clinical or serologic evidence of syphilis and has a completely normal spinal fluid at a period, say, of eighteen to twenty-four months after stopping treatment, the chances of neurosyphilis developing later on are probably negligible

To sum up, if a patient with early syphilis treated by one of these

intensive systems achieves a clinical "cure" immediately and a serologic "cure" within a short period following therapy (six to nine months), has a normal spinal fluid at some time during the second year after the treatment, and maintains this status of clinical and serologic "cure" for a period of five years after therapy, we have every reason to assume that the cure is complete and permanent. As the period of large-scale experimentation with intensive treatments began with the start of the five-day drip study in March 1938, a number of patients treated by these methods have already successfully passed this five years' test.

**Which Type of Treatment Intensive or Prolonged, Shall We Recommend to the Patient?**—The problem of which type of treatment, intensive or prolonged, to recommend to an individual patient with early syphilis cannot be so easily solved. In the first place, a great deal depends on one's estimation of the *reliability of the patient*. If one is dealing with large numbers of migratory patients who are of a low level of intelligence, uncooperative, and sexually promiscuous, without any doubt the common weal can best be served by the use of a system which can be administered in its entirety during a period of one or two weeks hospitalization, despite the known dangers inherent in such systems. However, by no means all individuals infected with syphilis, whether seen in clinics or in private practice are so unreliable and uncooperative. In our own clinic, which, because of its particular location in the city, draws a group of patients who are mainly laborers or white collar workers, we have found the average level of cooperation to be high. Among this group, 50 per cent of a series of 155 patients with infectious syphilis completed the full eighteen-months' Cooperative Clinical Group system of treatment, and an additional 25 per cent completed the forty-weeks' treatment considered by the Cooperative Clinical Group to be sufficient to prevent infectious relapses.<sup>22</sup> As many or even more of the patients seen in private practice are completely cooperative. It would be grossly unfair to subject these groups of patients to the added dangers of the more intensive systems, when equally good therapeutic results can be achieved by some prolongation of the treatment.

Just what will prove to be the ideal total length of such treatments is hard to say, but at the present time it would seem as if some period between six weeks and six months will prove to be the most satisfactory length for the arsenotherapy of early syphilis. It should be pointed out that there are practical limits to the period of time during which it is required that the patient receive more than one injection per week. We have found no particular difficulty in the triweekly schedule with cooperative patients. However it is doubtful whether triweekly schedules over a much longer period than eight or ten weeks or biweekly treatments for more than six months would prove to be feasible even in groups of reasonably cooperative patients.



As there is some evidence that the incidence of toxic encephalopathy is slightly higher in *pregnancy* than in the nonpregnant state,<sup>23</sup> we regard pregnancy, even when accompanied by early syphilis, as a contraindication to the use of an intensive system of arsenotherapy. Our policy is to treat all pregnant women who are syphilitic with the conventional continuous system throughout the entire duration of the pregnancy.

Despite the increased safety of the more prolonged "quick treatments" over the original five-day drip, and the fact that some intensive system is available in almost every locality with a center for the treatment of syphilis, these methods are still in an experimental stage and should not be used by anyone who is not thoroughly familiar with the arsenical therapy of syphilis.

### PENICILLIN IN EARLY SYPHILIS

At the meeting of the American Public Health Association in October, 1943, Dr. John F. Mahoney of the U. S. Public Health Service presented the preliminary results of a "pilot experiment" in which four patients with infectious syphilis were treated with penicillin.<sup>5</sup> All four patients had darkfield positive primary syphilis, three were seropositive at the beginning and the other developed positive serologic tests for syphilis during the treatment. Penicillin was given intramuscularly every four hours for a period of eight days, for a total dosage of 1,200,000 Oxford units. The immediate results, as judged by disappearance of the treponemas, healing of the surface lesions and reversal to negativity of the serologic tests, were as good as those previously observed by any other known method. If the promise held out by this preliminary report is achieved after more extensive study, it is almost impossible to be too enthusiastic about this demonstration. Thus far, the administration of penicillin to man has been remarkably free from toxic reactions so that, if it is proved to be effective against early syphilis, virtually all the hitherto troublesome problems of "quick treatments" for infectious syphilis will have been solved. Unfortunately, because of the small supply of penicillin available, and the great demand upon that supply for use against infections other than syphilis, it is probable that even if further studies confirm its usefulness against syphilis it will be a long time before it is available for general use in this field.

### LATENT SYPHILIS

Under this designation are those patients who have definite evidence of infection with syphilis either existing in the history or in the form of repeatedly positive serologic tests for syphilis, but who do not have any other evidence of the disease as shown by physical examination, fluoroscopy and x-ray of the aorta, and examination of

optic atrophy, severe tabetic pains, or in those with or without clinical evidence of neurosyphilis who have markedly abnormal spinal fluids. All others are given a trial on chemotherapy with trivalent arsenical sometimes supplemented with tryparsamide, with fever therapy later on if chemotherapy does not seem to be effective. On an average, the various systems used require two or three years of chemotherapy for completion, whether or not fever is used, and are adapted to a greater or lesser degree to the particular problem presented by the individual patient.

**Intensified Methods in Neurosyphilis**—Dattner and Thomas<sup>25</sup> are conducting a clinical study of a much shortened system for the treatment of neurosyphilis. This consists of induction of fever by malaria in the usual manner followed immediately on the termination of the malaria by daily injections of 0.060 gm. of mapharsen for a total period of only ten days. No further chemotherapy is given, and the spinal fluid is rechecked every six months. They assume that, if the spinal fluid cell count and protein return to and remain normal after this procedure, the syphilitic process is inactive and will probably continue to remain so. The possibilities resulting from this type of experiment and also from experiments with the combined simultaneous administration of arsenoxide and mechanically induced fever are intriguing and deserve further careful study. Unfortunately, however, it will take a period of some years of follow-up before the efficacy of these intensified systems can be proven.

**Surgical Treatment of Syphilitic Primary Optic Atrophy**—Another method of treatment in neurosyphilis which is under study at present is the surgical procedure of stripping the arachnoid from the optic nerves and chiasm in patients with syphilitic primary optic atrophy. This was introduced in 1937 by Hausman and his associates,<sup>26</sup> and some of their reported results have been quite favorable. Our own experience with the method has been quite limited. Only three of our patients, none of whom had associated tabes dorsalis, have been subjected to the procedure, and, in every one of the three, the situation was so complicated with other factors of the disease and the therapy, that no conclusions one way or the other are permissible. Since the evidence that fever therapy can arrest many cases of syphilitic primary optic atrophy is so well established,<sup>27</sup> we prefer to use it immediately in almost all cases of this condition. However, we are willing to try the surgical procedure in those patients whose atrophy is progressing despite fever, or in those with syphilitic optic atrophy who show no clinical evidence of associated tabes dorsalis, the reason for separating this latter group being that it might be more likely that the degeneration of the optic nerve would prove to be on a basis of constriction when there is no evidence of a degenerative process in the spinal cord.

## CARDIOVASCULAR SYPHILIS

Despite the fact that arsenical therapy has been used for thirty-three years on a large scale in the treatment of syphilis, the question as to its ability to alter favorably the course of aortic syphilis is in doubt. This almost incredible situation has developed partly because of ill-advised use of arsphenamine in the early days of arsenotherapy, and partly because of the general divorce of the internists from the specialists engaged in the treatment of syphilis. During the last decade, largely under the influence of Moore,<sup>28</sup> and of the Cooperative Clinical Group,<sup>29</sup> the cautious arsenotherapy of aortic syphilis has received much more widespread trial. The impression gained from these studies is that arsenotherapy is definitely worthwhile. However, because of the extreme variability in the natural course of aortic syphilis, it will require considerably more years of follow-up after arsenotherapy to settle the issue definitely. It has been well established, as mentioned above, that arsenical therapy given early in the course of the syphilitic infection will prevent the later development of aortic involvement even though such therapy was too inadequate to prevent neurosyphilis.<sup>19, 20</sup>

In our clinic, the patients with frank aortic syphilis, that is, with aortic regurgitation or aneurysm, actually receive more prolonged arsenotherapy than any other patients with syphilis. Our system, which is merely a modification of Moore's, consists of alternating courses of twelve weekly injections of an arsenical (neoarsphenamine or arsenovide) alternated with courses of four weekly injections of bismuth over a total period of four years with no rest periods. Before the initial arsenical course the patient is given ten or twelve weeks of bismuth and potassium iodide to guard against the possibility of reaction around the coronary ostia at the time of the first arsenical. All doses of bismuth are the same, namely 0.2 gm. of an insoluble preparation of bismuth subsalicylate. The initial doses of arsenical are tiny (0.05–0.1 gm. of neoarsphenamine or 0.010 gm. of mapharsen) and during the first twelve week course are gradually increased, never, however, going above 0.3 gm. of neoarsphenamine. During subsequent arsenical courses, if the patient has shown no evidence of untoward effects from the arsenical, the dose is gradually increased to full therapeutic levels (0.4 to 0.8 gm. of neoarsphenamine and 0.4 to 0.06 gm. of mapharsen) and maintained at those levels throughout the remainder of treatment. When the four years of continuous therapy have been completed the patients are given at least one course of twelve arsenical treatments each year thereafter. Patients in congestive heart failure are not treated until compensation has been restored.

Since this system has been in use for only a period of about six years, no conclusions are permissible in regard to its efficacy in arresting the aortic disease. However, it has been used sufficiently long

(in the treatment of over 100 patients with syphilitic aortic insufficiency) to form an opinion of its safety. Using the exact system as outlined above, we have never encountered any reactions such as the Herxheimer or "therapeutic paradox," which could be attributed to the harmful effect of the arsenotherapy on a syphilitic aorta. The only reactions which have been observed are those common to the arsenical treatment of syphilis in general, such as the development of skin sensitivity. It cannot be too strongly emphasized that, entirely apart from any theoretical untoward effect of arsenic on a syphilitic aorta, a patient with aortic syphilis with involvement of the valve or a coronary ostium has heart disease. Any patient with heart disease, regardless of the etiology, might not be able to tolerate one of the so-called minor reactions of arsenical therapy such as vomiting or diarrhea, which would represent no great danger to a patient with a normal heart. The administration of arsenic, just like the administration of any medication to a cardiac, must therefore be handled with caution, but when handled with such caution is a safe procedure.

#### SUMMARY

The recent advances in the therapy of syphilis have been almost entirely in the field of the more rapid treatment of early syphilis. Fundamental information about arsenotherapy which has been established by the study of these intensive systems in animals and in man is being applied to the treatment of late latent syphilis. The treatment of neurosyphilis is still a prolonged affair despite the greater use of fever therapy. Experimental studies on various combinations of simultaneous fever and chemotherapy may, however, eventually lead to a shorter system of treatment here also. Arsenotherapy of aortic syphilis is a perfectly safe procedure provided that the reasonable caution needed in the treatment of any cardiac is used. Whether it can arrest the progress of the aortic disease is still not established, but its use for this purpose deserves further extensive trial.

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## ADVANCES IN THE STUDY AND TREATMENT OF RHEUMATOID ARTHRITIS AS REPORTED IN 1942 AND PART OF 1943

CHARLES H SLOCUMB, M.D,\* AND HOWARD F POLLEY, M.D †

AMONG the noticeable effects of this war on medical progress has been the stimulation of investigation in such fields as tropical diseases and aviation medicine. From a comparative standpoint, this is reflected as a decrease of the amount of investigation of the rheumatic diseases. Yet the lack of much desirable factual information and the chronicity of some of the clinical entities comprising this field of study make it increasingly important that physicians keep abreast of current studies. For many physicians the demands of either military or wartime civilian practice make this impossible. This résumé of the contributions to a fuller understanding of rheumatoid arthritis published in 1942 and part of 1943 may help to obviate this deficiency.

Not only is rheumatoid arthritis the most frequent cause of the rheumatic symptoms of patients seen by consultants in arthritis in civilian practice but it is also the most difficult to control. While persons in whom this disease has developed are eliminated from military service, rheumatoid arthritis makes its appearance among military personnel and may be expected to develop in increased frequency.

### CAUSE

The cause of rheumatoid arthritis is unknown. Hypotheses that have been advanced regarding its cause (infectious, metabolic, endocrine, circulatory, neurogenic) are not generally accepted.<sup>27</sup> Serum of patients who had rheumatoid arthritis agglutinated hemolytic streptococci in a higher percentage (58 per cent in a titer of 1/160 or more) than that of controls (13 per cent) and of patients who had osteoarthritis (28 per cent) but this difference could not be regarded as diagnostic or of etiologic significance.<sup>16</sup> Dienes and Smith cultured pleuropneumonia like (L) organisms from prostatic secretion, urethra, cervix or vagina of twenty-three of 129 patients. Two had rheumatoid arthritis, one had polyarticular swelling and four had soreness in fibrous tissue and muscles. No organisms were obtained from the synovial fluid of one patient. This interesting observation needs further study. Angevine, Rothbard and Cecil could find no significant organisms in culturing blood, joint fluid, synovia or subcutaneous nodules.

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From the Division of Medicine, Mayo Clinic, Rochester, Minnesota.

Assistant Professor of Medicine, Mayo Foundation, University of Minnesota.  
Consultant in Division of Medicine, Mayo Clinic.

† Consultant in the Division of Medicine, Mayo Clinic.

## STUDY AND

similar in microscopical  
nodules of patients

Four studies on three papers in which cardiac lesions indistinguishable from those reported in sixteen of the three (Bayles<sup>5</sup>) and The high incidence of rheumatic fever suggests that rheumatoid arthritis not only has cardiac lesions of the type seen in rheumatic fever, but few exceptions, and that the changes from rheumatoid arthritis to rheumatic fever are very different and that the changes in the nodules are very different. It is apparent that the usual changes in the nodules of rheumatoid arthritis differ so markedly from those of rheumatic fever that the pathogenesis of the nodules can be inferred that the pathogenesis of the nodules is, therefore, in the absence of any other evidence, seem advisable to consider rheumatoid arthritis as separate from rheumatic fever.

TREATI

The permanency of building up the patient can be discussed. The patient to improve general health and fibrous tissue contractures and muscular rheumatoid arthritis. The opportunity to build up the active disease after control of the active disease.

1 Help for the Patient

essential in controlling an acute or subacute stage of chronic rheumatoid arthritis. The affected joints should be kept in case some residual movements should be performed. The patients showing progressive and continue with work, even in this group, to

## Help for the Patient



similar in microscopic structure to the more obvious subcutaneous nodules of patients who have rheumatoid arthritis

Four studies on necropsies totaling 162 cases were reported. In the three papers in which details of the cardiac findings were given cardiac lesions indistinguishable from those of rheumatic fever were reported in sixteen of thirty (Baggenstoss and Rosenberg), six of twenty-three (Bayles<sup>5</sup>) and nineteen of sixty-one (Fingerman and Andrus). The high incidence of cardiac lesions indistinguishable from those of rheumatic fever suggests a relation between rheumatic fever and rheumatoid arthritis not yet understood, yet it must be stressed that the cardiac lesions of the patients who had had rheumatoid arthritis, with but few exceptions, were mild. Clinical study of patients suffering from rheumatoid arthritis shows only a few that have diagnosable cardiac lesions (Rosenberg), the clinical courses of the two diseases are very different and the changes in the joints and the microscopic changes in the nodules are different. Bennett concludes that "It is apparent that the usual anatomic changes observed in rheumatoid arthritis differ so markedly from those of rheumatic fever that one must infer that the pathogenesis of the observed lesions is different. Therefore, in the absence of etiological evidence to the contrary it would seem advisable to continue to look upon rheumatic fever and rheumatoid arthritis as separate and distinct entities."

#### TREATMENT OF RHEUMATOID ARTHRITIS

The permanency of arrest of active rheumatoid arthritis depends on building up the patient's resistance to control the disease. The treatment can be discussed under three main headings: (1) help for the patient to improve general resistance; (2) proper care of joints, muscles and fibrous tissue to minimize damage in the joints, deformities, contractures and muscular atrophy; (3) temporary control of the active rheumatoid arthritis in the hope that this will give the patient an opportunity to build up his resistance sufficiently so that he can control the active disease after the treatment has been discontinued.

1. *Help for the Patient to Improve General Resistance*—Rest<sup>1, 2, 3, 4</sup> is essential in controlling an active phase of rheumatoid arthritis. During an acute or subacute stage of the disease or during a period of progression of chronic rheumatoid arthritis considerable rest in bed is advisable. The affected joints should be placed in the best position<sup>4</sup> in case some residual limitation of movement develops. Supervised movements should be performed each day to preserve adequate range of movements in the joints. Patients who have less severe arthritis and patients showing progressive improvement may be moderately active and continue with work provided the affected joints are not traumatized even in this group ten hours of rest at night and a midday rest

period are advisable. The rest must be both physical and mental. Without this rest, the patient cannot put up his best resistance against the disease.

Analgesic agents such as acetylsalicylic acid<sup>20</sup> (aspirin) or sodium salicylate given in 10 grain (0.65 gm) doses with an equal amount of alkali are often necessary for adequate rest. The dose may be repeated every four to six hours. Acetophenetidin, aminopyrine and cinchophen may be used for short periods but because of slight risks of toxicity they should be avoided if acetylsalicylic acid or sodium salicylate is adequate for the control of pain. Local applications of heat, counter-irritants or careful movements to "lumber up" the painful region may give sufficient relief. Even though the foregoing measures need to be repeated every three to four hours during the night, one should do this rather than resort to narcotics. Mild sedatives in addition to the analgesics may give more relief than an analgesic alone but it is usually best not to give the sedatives without some analgesic to control the pain.

Mental rest<sup>12, 24, 30</sup> is also very important. The patient must have confidence that the attending physician is following a schedule of accepted treatment and will be willing to make changes if such should be indicated. The patient does not have the right to expect a change of treatment every few days or even with minor transitory flare-ups and must be willing to work with the physician in evaluating progress. The physician must keep an optimistic but realistic understanding with the patient and should give the patient insight into the problems of his disease.

A well-balanced<sup>6, 37</sup> diet should be advised for patients who have rheumatoid arthritis. The diet should be high in vitamins and minerals and adequate in proteins and should have calories according to the patient's weight. The patients that are undernourished should be urged to eat irrespective of appetites so that a high caloric intake is assured. The obese patients should reduce slowly to prevent added injury to their weight-bearing joints. Pemberton lists the abnormalities of the gastro-intestinal tract encountered among patients who have arthritis and suggests that supplemental B complex should be given to them. Freyberg<sup>19</sup> well summarizes the value of each of the known vitamins in the treatment of rheumatoid arthritis. There is no specific value in any of them although the requirement for vitamins of a patient who is sick is often greater than that of a normal person. When the patient's diet cannot be well controlled, vitamin supplements may be given. Discussion of vitamin D will be presented later.

Removal of foci of infection cannot be regarded as the removal of the cause of rheumatoid arthritis and should be carried out conservatively, in cases in which such removal will improve the patient's general resistance.<sup>37</sup> Boots and McCollom report that improvement usually

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Transfusion of 250 to 500 cc. of blood may shorten the convalescence in cases of rheumatoid arthritis in which anemia will not respond to the administration of iron

2 *Proper Care of the Joints, Muscles and Fibrous Tissue*—Physical therapy cannot be dispensed with in the successful treatment of rheumatoid arthritis.<sup>37 38</sup> It is the oldest and one of the most valuable forms of treatment for these patients. An appropriate amount of rest has been stressed and is essential but in addition daily slow purposeful movements (not purposeless wiggling of joints) are essential if the intra-articular adhesions and extra-articular fibrous and muscular contractures are to be kept from depriving the patient of a useful (even though not normal) joint. These movements can be carried out most easily after heat has been applied to the affected region. The local application of heat relieves pain, muscle spasm and subjective stiffness and it increases the circulation to the affected area. Light massage over the muscles with the stroke directed to help the return flow of venous blood also aids in circulation and relaxation. Krusen<sup>3</sup> and Solomon<sup>41</sup> have described very practical means of giving the physical therapy. Owing to the cost of professional physical therapy and its unavailability in many places it is essential to enlist the careful co-operation of the patient in having him and his family carry out the simpler forms of exercises, applications of heat and sometimes even massage to supplement such supervised treatment as is available. Treusch and Krusen have found that four out of five of the patients so instructed felt that their own home efforts were of definite additional help.

During periods of rest the joints should be placed in the best position in case there is limitation of movement in spite of efforts with physical therapy. Joplin and Baer describe and demonstrate with photographs various ways of splinting joints and the use of corsets and braces.

If the affected joints are improving and can tolerate it the patient's work may be his form of occupational therapy. However, supervised occupational therapy may be very helpful in treatment of patients whose joints cannot tolerate usual activities but for whom efforts should be made to keep up muscular strength or increase the range of movement of the joints. Any occupational therapy should be aligned closely with the physical therapy that the patient is receiving. Blodgett presents the "place of occupational therapy in the treatment of arthritis."

3 *Temporary Help in the Control of Rheumatoid Arthritis*.—There are many remedies that have been advocated as being of some help. Most of these have been discarded others have a definite place in the treatment of patients whose rheumatoid arthritis is difficult to control.

Fever therapy produces an apparent improvement of symptoms for hours or a few days. If it is repeated, significant help may be observed in some cases. The fever therapy may be given in any of many ways (cabinet, diathermy, baths, packs or typhoid vaccine). Osborne and his associates prefer to induce a fever of 104° F for four hours although we prefer to raise the body temperature to 100 to 102° F for half an hour and to give the treatment about three or four times a week. Fever therapy should be given only if the patient's general condition warrants its use and should not be repeated until the patient has recovered his strength and weight after the treatment.

No climate<sup>25</sup> is a cure for patients who have rheumatoid arthritis although some of them feel better in a warm or preferably a warm dry climate.

**VITAMIN D**—Large doses of vitamin D have been used in the treatment of rheumatoid arthritis since 1935. The pendulum swing of popularity of vitamin D for the treatment of this disease has now gone far beyond its rightful place. Enthusiastic advertising and publicity have overemphasized part truths and overlooked the rest of the available information. In 1942 and 1943 there are six reports on five series studied (Table 1). In four of the five series, Ertron was used, in the other report three other preparations of vitamin D were used.<sup>33</sup>

TABLE 1—VITAMIN D IN THE TREATMENT OF RHEUMATOID ARTHRITIS\*

Authors	Cases	Results of Treatment			Dose Units Vitamin D	Toxicity
		Excellent	Good or Fair	Slight or None		
Snyder and others <sup>14,16</sup>	24 rheumatoid	6 (25%)	13 (54%)	5 (21%)	100,000 to 500,000 av 200,000 Ertron	None serious, "few" nausea and vomiting, elevated non-protein nitrogens of 46 to 60 disregarded by authors.
Wagner <sup>18,19</sup>	32 of Snyder's cases	5 (16%)	20 (62%)	7 (22%)	Ertron	From foregoing series.
Freyberg <sup>12,21</sup>	36 with 45 courses		14 (39%)		25,000 to 400,000 Ertron	8 (22%) anorexia and vomiting; 3 (8%) polyuria, 1 with renal impairment.
Kelchner	40		22%		Ertron	6 (15%) refused to continue; 3 joints worse; 1 headache; 1 abdominal pain; 4 (10%) discontinued for apparently unrelated causes.
Steck	98 mixed	14 (14%)	76 (78%)	8 (8%)	Ertron	None
Slocumb	14 rheumatoid		7 (50%)		52,500 to 386,000, 3 different preparations	12 of the 14 patients nausea, vomiting, occipital headaches. Polyuria, polydipsia. Renal impairment in 6 cases.

\* Levinthal and Logan also used Ertron but carried out so much other treatment that it is difficult to evaluate the effectiveness of Ertron in their series.

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The toxicity of vitamin D varies somewhat with various preparations. Early signs of toxicity<sup>38</sup> are sweet taste, nausea, vomiting, polyuria, polydipsia and occipital headache. If these early signs of toxicity are ignored, significant renal damage may occur with elevation of the concentration of urea in the blood and of nonprotein nitrogen in the serum and the appearance in the urine of albumin and casts. If toxic symptoms are respected and administration of vitamin D is discontinued with their appearance, no apparent permanent damage is produced. Steck does not report any toxic reactions after administration of ertron. Snyder and his associates<sup>45-49</sup> do not report any serious toxic reactions but they observed nausea and vomiting in a "few" cases. They disregarded elevations of the nonprotein nitrogen to 46 to 60 mg per 100 cc of serum in some of their cases. After administration of the same preparation, ertron, Freyberg<sup>19-21</sup> noted anorexia or vomiting in eight cases (22 per cent) and polyuria in three (8 per cent). Renal impairment developed in one of the cases in which there was polyuria. Kelchner stopped administration of vitamin D to 25 per cent of the patients treated as listed in Table 1. Usually from 150,000 to 300,000 units of vitamin D daily have been used and in this range of dosage it may be toxic. Any patient getting large doses of vitamin D should be warned of its toxic symptoms so that administration can be discontinued promptly should such toxic symptoms occur.<sup>38</sup>

There is considerable difference of opinion as to the value of large doses of Vitamin D in the treatment of rheumatoid arthritis. Steck reports excellent results in 14 per cent and fair to good results in 78 per cent of patients treated. The figures of Snyder and his associates<sup>45-49</sup> are a little less impressive. Freyberg<sup>19</sup> and Kelchner noted significant improvement in 39 per cent and 22 per cent respectively. One of us<sup>38</sup> noted improvement in half (seven of fourteen) of the patients treated. Flare-ups may occur during the treatment. Vitamin D is not a specific remedy for rheumatoid arthritis but in some cases (average about 50 per cent) improvement of symptoms is present during the time vitamin D is given. Objective improvement and a drop of the sedimentation rate of red blood cells occur less frequently. When vitamin D does produce improvement, its beneficial effect is lost within a few weeks of the time its administration is discontinued,<sup>19-24</sup> although a few patients<sup>49</sup> may maintain the improvement without the additional help of vitamin D after its administration is stopped.

Large doses of vitamin D may be worth a trial in the treatment of rheumatoid arthritis provided toxic symptoms are respected and the medication is discontinued or the dose markedly decreased. Its use alone without established measures of proved value is not justified. Vitamin D can be regarded as one of several schedules of treatment supplemental to conservative programs which may be tried if conservative treatment alone is inadequate.

**GOLD SALTS**—Gold salts have been used in the treatment of arthritis since 1927. Their proper place in the treatment of rheumatoid arthritis has not yet been established but progress in the study of their therapeutic value, toxicity, dosage and mode of action is being made.

Preston, Block and Freyberg have demonstrated that it is the gold (not the sulfur) in the salts that is the active ingredient in the treatment of a form of arthritis produced in mice by pleuropneumonia like organisms. Cecil, Kammerer and dePrume<sup>13</sup> cite their own work previously reported and the work of others showing that gold salts have a chemotherapeutic effect (bacteriostatic) on *Streptococcus haemolyticus* and pleuropneumonia-like organisms. Since the cause of rheumatoid arthritis is not known, it cannot be assumed that the therapeutic results in the treatment of rheumatoid arthritis are explained satisfactorily.

Freyberg, Block and Wells<sup>22</sup> have demonstrated that most of the gold is retained in the body for weeks or months and is excreted gradually through the kidneys, only a very small amount appearing in the feces. The aqueous solution of gold sodium thiomalate (myochrysine) for intramuscular injection contains 50 per cent of gold. During a course of treatment, 75 to 85 per cent of the gold in myochrysine<sup>20, 22</sup> is retained and this is excreted gradually over a period of a few months to a year or more. Gold sodium thiosulfate is an aqueous solution for intravenous injection and contains 37 per cent of gold. A larger total dose of the salt is required to get in the same amount of gold and during the first few hours after an injection of the salt the excretion of gold is a little higher than when gold sodium thiomalate is used. Gold thioglucose (solganal-B oleosum) for intramuscular injections contains 50 per cent of gold. It is absorbed more readily than myochrysine and, in order to have an amount of gold retained equal to that retained from the similar injections of myochrysine, about 150 per cent of the dose for myochrysine is required if gold thioglucose is given. Colloidal gold sulfide (aurol sulfide) is a colloidal suspension containing 87 per cent of gold. More than 99 per cent of it given intramuscularly or intravenously is retained in the body but in the colloidal state it has much less therapeutic value than the preparations of soluble gold salts.

The results of treatment have not produced any uniformity of opinion as to the place gold salts should have in the treatment of rheumatoid arthritis. Some authors regard gold salts as the best available treatment for rheumatoid arthritis, others regard their use as justified in only a few cases because of inconclusive beneficial results and high risk of toxicity. Rosenberg has tabulated the results of treatment by twenty-two of the American and British authors. Short collected reports from the literature on 1800 cases in which gold treatment was used. Cures (arrests) were reported in 13 per cent and marked im-

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provement in 63 per cent. In Table 2 the percentage of improvement proximate these results among the patients treated with gold salts.

TABLE 2.—REPORTS IN 1930

Authors	Results
Cecil, Kammerer and dePrume	Early, Late
Price and Leichtentritt	Mild, Moderate, Severe
Short <sup>22</sup>	3
Furlong	1

TABLE 3.—RELAPSES AMONG PATIENTS WHO WERE CURED

Authors	Relapses
Cecil, Kammerer and dePrume	Remission, Great, Moderate
Price and Leichtentritt	Mild, Moderate, Severe
Short	

cases in controlling the rheumatoid process. It is apparent that relapses are common. Usually, however, the patients who relapse after gold salts is given. Gold, like

provement in 63 per cent, yet Short's work with Bauer did not approximate these results

In Table 2 the percentages of remissions and of great improvement among the patients treated with gold show that it is of value in some

TABLE 2.—REPORTS IN 1942 AND 1943 ON GOLD SALTS IN THE TREATMENT OF RHEUMATOID ARTHRITIS

Authors	Cases	Remissions	Greatly Improved	Moderately Improved	Not Improved
Cecil Kammerer and dePrume	Early 51	20 (39%)	20 (39%)	5 (10%)	6 (12%)
	Late 146	42 (29%)	48 (33%)	34 (23%)	22 (15%)
Price and Leichtentritt	Mild 14		13 (93%)		
	Moderately advanced 30		24 (80%)		
	Severe 37		23 (62%)		
Short <sup>14</sup>	31	6 (19%)			
Furlong	16	1 (6%)	9 (56%)	2 (13%)	4 (25%)

TABLE 3.—RELAPSES AMONG PATIENTS WHO HAD RHEUMATOID ARTHRITIS AND WHO WERE TREATED WITH GOLD SALTS

Authors	Response to Treatment or Type of Case	Patients	Relapses	
			Number	Per Cent
Cecil Kammerer and dePrume	Remission	62	21	34
	Greatly Improved	68	34	50
	Moderately Improved	9	13	
Price and Leichtentritt	Mild	13	3	23
	Moderately advanced	21	11	52
	Severe	23		90
Short		6		50

cases in controlling the rheumatoid arthritis. From Table 3 however it is apparent that relapses after the treatment are often present. Usually however the patients will improve again if a second course of gold salts is given. Gold like much of the other treatment for rheu

matoid arthritis, is a temporary help to control the rheumatoid arthritis but, because the gold is retained in the body for months, improvement from gold, if it occurs, usually lasts for several months

(a) *Toxicity*—The high toxicity of gold for some persons is the greatest drawback to its use Short's review of the reported cases in the literature shows that one person in 200 (0.5 per cent) of the patients given gold died as a result of the injections of gold Three deaths from toxicity of gold were reported in 1942, one from enteritis<sup>13</sup> and two from thrombocytopenia with purpura<sup>34, 44</sup> Significant toxicity was present in 42 per cent,<sup>13</sup> 38 per cent,<sup>34</sup> 74 per cent<sup>36</sup> and 81 per cent<sup>23</sup> of the patients However, Cecil<sup>12</sup> and Freyberg and others<sup>22</sup> express the belief that serious toxic reactions occur among somewhat less than 10 per cent of the patients treated The most common significant toxic reaction is dermatitis When severe, it may be an exfoliative dermatitis Less commonly encountered are stomatitis, albuminuria or hematuria, enteritis, bronchitis, neuritis, jaundice and particularly damage to the bone marrow as evidenced by agranulocytosis or thrombocytopenia with purpura and hemorrhages One case was reported in which a toxic reaction developed after the patient had received only 25 mg of gold salts, although most reactions that occur are in the latter part of the course or even after the course has been completed In spite of special studies on the treatment of toxic reactions, no effective treatment is yet available<sup>22, 47</sup> The mild reactions disappear in a few weeks but severe reactions may remain for months

(b) *Dosage*—The dose used by various investigators has varied from 10 mg to 200 mg of the gold salt per injection each week Cecil, Kammerer and dePrume<sup>13</sup> compare their results obtained after giving various sized doses and different total amounts of the gold salts They observed that the size of the individual dose did not have much effect on the results of treatment The size of the total dose given was much more important than that of the individual dose A total amount of gold salts of 1 gm or more for a course of treatment gave the best results Generally 50 to 100 mg of the gold salt was given weekly after gradually working up to that dosage

Freyberg<sup>20, 22</sup> found that, when 100 mg of gold sodium thiomalate (myochrysine) (equal to 50 mg gold) was given weekly, the toxicity was significantly greater and the therapeutic value only slightly better than if 50 mg of this gold salt (25 mg gold) was given weekly If 25 mg of gold sodium thiomalate (12.5 mg gold) was given weekly, the toxicity was less but the therapeutic value was also much less Freyberg urges a weekly dose of 50 mg of gold sodium thiomalate or its equivalent, that is, 65 mg of gold sodium thiosulfate or 75 mg of solganal-B oleosum, taking into consideration the gold content and the speed of excretion

(c) *Conclusions on the Use of Gold Salts*—We must conclude that



gold is so toxic to patients that it should not be given until after a trial of from one to three months of conservative treatment and that then it should be given only in case of progression of the arthritis in spite of conservative treatment, and only with a full understanding by the patient of the risk and only to a patient who is willing to co-operate with the physician during the treatment to report any symptoms of pruritus or itching, stomatitis, gastro-intestinal upsets or dermatitis. It is also safest to obtain a specimen of urine, a leukocyte count and a platelet count every week. Gold should not be given by a physician unless he is familiar with the bad as well as the good results. The articles by Freyberg, Block and Wells and by Cecil, Kammerer and dePrume are recommended for a more complete understanding of the use of gold salts in the treatment of rheumatoid arthritis.

**OTHER FACTORS CAUSING IMPROVEMENT**—In 1942 and 1943 there have been no available reports on the improvement in rheumatoid arthritis during jaundice or pregnancy and only two short reports on vaccine<sup>10 11</sup>

*Histamine* and *mecholyt iontophoresis* may be of value in treatment of rheumatoid arthritis to produce temporary improvement for only a very short time. Smyth and Freyberg noted some improvement after treatment in 79 per cent of cases but on re-examination only 11 per cent maintained any of the improvement. Simpler and less expensive procedures than iontophoresis produce equally good results. Much the same local vasodilatation can be produced by mild fever treatments. Bee venom<sup>14</sup> may relieve pain partially but has very little if any effect on systemic manifestations of rheumatoid arthritis. Cobra venom<sup>12</sup> has very little effect on the symptoms or progress of rheumatoid arthritis.

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# CHRONIC DISEASES OF THE LARYNX AND TRACHEA

## Pitfalls in Diagnosis and Treatment

CHEVALIER JACKSON, M D , F A C S \*

AND

CHEVALIER L. JACKSON, M D , F A C S †

CHRONIC diseases of the larynx and trachea are common and among them are many of the most serious that affect human beings. We have gathered together a group of cases that will illustrate some of the most commonly encountered of these diseases, and a few of the many that are beset with *pitfalls for the medical practitioner*.

### TUBERCULOSIS OF THE TRACHEAL WALL WITHOUT PULMONARY INVOLVEMENT

CASE I—This girl is eighteen years of age. She has been referred to us for examination of the larynx and trachea by the Medical Out-Patient Department because a suspicion of possible pulmonary tuberculosis remains entirely unsupported. The patient has an occasional dry cough but there has been no detectable fever, no weight loss or abnormal physical signs, the scant sputum obtained after the administration of potassium iodide was negative, the roentgen-ray examination of the chest was entirely negative, the apices being especially clear.

Our laryngeal mirror examination showed no abnormality. On putting down a bronchoscope we found in the lower part of the cervical trachea an epithelial erosion on an infiltrated, growthlike base. We took a specimen of tissue. Microscopic examination of the specimen showed the typical giant-cell structure of tuberculosis, and tubercle bacilli were, after much effort, demonstrated in the tissue.

The diagnosis therefore is definitely *tuberculosis of the tracheal wall without pulmonary involvement*.

Comment—The question naturally arises as to *why sputum examination had been repeatedly negative* in this case when there was an active tuberculous lesion on the tracheal wall.

A partial explanation is that the sputum was scanty, had there been a breaking down, freely discharging lesion the chances of finding bacilli in the sputum might have been somewhat better, but, anyway, it is a curious clinical fact frequently observed at the Bronchoscopic Clinic that in cases of tuberculosis of the wall of the tracheobronchial tree, with no demonstrable lesion of the pulmonary parenchyma, the sputum is practically always negative for tubercle bacilli.

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\* Honorary Professor of Broncho-Esophagology and Consultant in Research, Broncho-Esophagologic Research Laboratories, Temple University Medical School, Philadelphia

† Professor of Broncho-Esophagology and Director of Broncho-Esophagologic Research Laboratories, Temple University Medical School, Philadelphia

*Treatment* is of utmost importance. As in all cases of tuberculosis, primary consideration must be given to medical care and management. Though the lesion is quite accessible, and though there is no contra-indication to local treatment, we must not lose sight of the fact that pulmonary tuberculosis will certainly develop unless the strictest kind of antituberculous regimen is instituted, including rest in bed outdoors for say, fifteen hours out of the twenty-four, to increase the patient's resistance. All other details of an antituberculous regimen should be carried out as if the patient had incipient tuberculosis of the pulmonary apices.

One local measure is important. The patient is an incessant talker. She should be restricted to 100 words a day, and this order should be specific and rigidly enforced, to guard against laryngeal tuberculosis. It is utterly useless merely to tell a talkative patient not to talk so much.

#### CARCINOMA OF THE LARYNX

**CASE II**—The patient is a man aged thirty two years. The chief complaint in this case is hoarseness of many years duration. A diagnosis of chronic laryngitis was made by a number of reputable physicians, some of whom made a casual examination of the larynx. Roentgen ray studies of the chest were repeatedly negative. The patient is in good general health and except for the hoarseness and an occasional clearing of the throat, as he calls it, he is symptom-free.

On palpation of the neck no nodes are found but on palpation of Adam's apple we detect a broadening of the anterior part of the thyroid cartilage and a fullness and firmness of the usually depressed and yielding cricothyroid membrane.

We have examined the larynx in the usual way with the mirror. At first we saw nothing much amiss. There was certainly no evidence of chronic laryngitis in the part of the larynx easily visible. After repeated mirror examinations we were able to see the anterior wall and there, at the base of the epiglottis and extending down into the anterior commissure and upper part of the trachea, was a diffuse infiltration with an eroded surface suggestive of tuberculosis, syphilis, or malignant disease.

Serologic tests and general medical examination being negative, we took a specimen of the growth and the histologic examination shows a *carcinoma* of the aggressive type known as Grade 4.

**Comment**—The choice of *treatment* in this case lies between operation and irradiation. If this lesion were a small one near the middle of a vocal cord, the chances of cure on a statistical basis would be 80 per cent. But here we have an extrinsic growth extending from the base of the epiglottis down onto the anterior wall of the trachea and, moreover, the histologic study shows a high degree of malignancy. In such cases the results from operation are nothing like so good as in early small intrinsic cancer. Another point against a favorable result from operation is that growths at the base of the epiglottis usually are accompanied by leakage of the malignant process into the base of the tongue, where complete excision is usually impossible.

On the other hand, the conditions are most favorable for irradiation. The cellular type is of the fourth grade, that is, the type showing least

differentiation, least keratinization, and least pearl formation, with most numerous mitotic figures. This histologic type is the most sensitive to irradiation. It is true that it is the type in which the percentage of recurrences after irradiation is greatest, but operation has nothing better to offer when, as in this case, the growth is extrinsic. For emphasis it is necessary to repeat, in making this statement, that we are not referring to early intrinsic cancer of the larynx, in which there is freedom from recurrence after laryngofissure in over 80 per cent of the cases.

In addition to the histologic type of growth there is another feature of this case that is favorable for irradiation. The growth is all on the anterior wall of the larynx and upper trachea, and is relatively superficial, almost under the skin, one might say. In this anteriorly projecting region far anterior to the spine, the growth can be efficiently irradiated by crossfiring from practically all directions.

As between radium and the roentgen ray the decision, in this kind of case, may well rest upon which agent is the more readily available. Equally good results, in cases of growths in precisely this location, have been obtained by use of each of these sources of radiant energy. With any method of irradiation the utmost care is necessary to avoid the excessive dosage to the thyroid and cricoid cartilages that is certain to result in utter destruction of the larynx by ravages of suppurative perichondritis and necrosis of these radiosensitive structures. At cancer age these cartilages are partly ossified and the ossific areas are prone to stop and absorb a lethal quantity of the radiant energy.

By way of further comment it should be added that, though many cases of chronic laryngotracheal disease require nothing more than general medical care and management, as we will show in other cases, treatment should not be instituted on the basis of a diagnosis of chronic laryngitis made without thorough examination of the larynx, and such examination is never complete unless the anterior commissure is visualized. The pitfall in this case was that the growth was hidden from mirror view under an overhanging epiglottis.

Another point illustrated is the value of *palpation of the larynx and cervical trachea* in diagnosis. Of course, palpation of the neck for nodes, goiter and other tumors is a routine part of any medical examination, but few practitioners avail themselves of the trained touch in the palpation of laryngeal and upper tracheal cartilages. The presence of a new growth was revealed unmistakably by proper palpatory examination, in this case.

#### CHRONIC TRACHEITIS WITH MOSS-AGATE SPUTUM

CASE III.—This man, who is forty-two years of age, presents somewhat the same problem as the first patient. He is suspected of pulmonary tuberculosis but supportive evidence is lacking. There is no detectable fever, no weight loss, and the

physical signs and roentgen ray examination are entirely negative. The cough is at times annoying but rarely productive. The patient states that at times he is hoarse, but he will then clear the voice by bringing up a small pellet of pearly-looking starchlike sputum mixed with soot or black dust. He says it is never yellow never looks like pus and he has never noticed any streaking with blood. After raising a pellet of this peculiar sputum, his voice usually remains clear for a few hours.

On examination we saw some of the peculiar secretion bridging across both vocal cords and clinging to the posterior commissure. By encouraging the patient to continue clearing his throat we obtained from him a specimen of secretion. On gross examination it was found to be short that is to say that, though adherent, it broke apart like boiled starch and did not pull out in strings. It was somewhat translucent, not opaque like pus. In it were irregular streaks of dark material like the streaks in the gem known as a moss agate. Here we had typical moss agate tracheal sputum as it has been well named. As a matter of routine we had the usual bacteriological examination of sputum. It was not unexpected when the secretion was found to contain no tubercle bacilli, and only a few bacteria insignificant in kind and number.

Examination of the trachea with the bronchoscope revealed a chronically inflamed mucosa, glazed and patchy red in color; the ringed appearance was less sharp than normal; branching vessels were conspicuous in some locations invisible in others. Here and there were pellets of secretion apparently similar to the secretion examined.

From the endotracheal appearances, the typical moss-agate tracheal secretion the symptoms and the negative general findings we made the working diagnosis of *chronic tracheitis*.

**Comment**—Such a diagnosis forms the basis for *treatment* but it should not be taken as *final* nor as *conclusive* against *sequelar disease*. Such a patient requires periodical watching for an indefinite period and meanwhile he can be cured of the chronic tracheitis by appropriate treatment.

What is appropriate treatment for such a case? The ideal treatment for chronic tracheitis is for the patient to change his residence to a warm moist seashore climate. This is not practicable in many cases. Such a change of residence is contraindicated in any patient suspected of susceptibility to tuberculosis, but in a patient with chronic tracheitis a prolonged sojourn in such a climate will be at least temporarily beneficial and often curative.

A dusty occupation should be abandoned or a protective mask should be worn. Nasal breathing should be restored, if impaired as it usually is, even though operation be necessary for restoration. Avitaminosis, if present, should be cured by correction of the diet and the administration of vitamin medication.

The best local application is mono-*p*-chlorphenol, 1 per cent solution in liquid petrolatum. This drug is made by the Eastman Kodak Company. The 1 per cent solution should be inhaled as a spray from an atomizer with a nozzle to direct the spray downward into the larynx. As with all other phenols caution against excess dosage is nec-

essay. Once a day is the limit of frequency and the total amount of spray should be limited. It would be better for the physician, himself, to make the applications, say about thrice weekly, if the patient is not trustworthy.

The *prognosis* in this case is good, but recurrences in such cases are likely if the patient is long exposed to dry, dusty atmospheric conditions.

Incidentally, it is interesting to note that the dark, fuzzy irregular streaking that justifies the name of "moss-agate" tracheal sputum is not soot or black dust from the inspired air. It is hemosiderin derived from phagocytic cells of the blood.

**Other Varieties of Chronic Tracheitis**—By way of comment it might be well to mention the fact that there are varieties of chronic tracheitis other than this common kind. There is the *atrophic tracheitis* in which crusts are expectorated. They can be seen in the laryngeal mirror clinging to the tracheal wall. This type of tracheitis is best treated in the same way as the preceding form, but the prognosis is not so good because the mucosal glands are atrophied.

Another variety is the *chronic membranous tracheitis* in which shreds of membrane, or sometimes casts, are expectorated. The laryngeal mirror repeatedly used will eventually reveal a mass of membrane coming up to the posterior commissure. This type of tracheitis is usually due to a specific bacterial infection. If this infective agent can be discovered by examination of the secretion or membrane, an autogenous vaccine will be curative. Lacking this, the treatment mentioned in connection with this case will be helpful.

#### MYASTHENIA LARYNGIS

**CASE IV**—Here we have the case of a man, aged thirty-two years, a down-and-out professional singer who has lost his voice. His chief complaint is a wrecked career due to hoarseness and what he calls cracking and breakdown of his voice when he attempts to sing in public.

The patient being now beyond hearing distance we may discuss his case freely. It is a common kind of trouble. It may be said that probably a half or three fourths of the professional vocalists go the same way, unless they abandon the vocal career before the breakdown develops.

This patient has been told many times that he had chronic laryngitis. He certainly has no chronic laryngitis now, and it is doubtful if he had it at other times, though of course it cannot now be said what was or was not present in this case before our examination. We have, however, seen many similar cases in which an erroneous diagnosis of chronic laryngitis was made.

When we examined this patient's larynx we found the mucosa normal. When we asked the patient to make a tone of any pitch and to hold it for the longest possible time he would strike the tone with the normal *coup de glotte*, as the singers call it, but instead of being able to hold it, as any singer normally can, the voice would break. That is to say, the tone would suddenly drop in pitch, become rough and weaken, or, at other examinations, gradually fade out and

we had the patient repeat this performance with the laryngeal mirror



in place we saw the normal approximation and vibration of the cords when the tone was struck but instead of this tone being held as a normal singer would hold it, and as no doubt this patient in better days could hold it, the cords relaxed and then parted synchronously with the breaking of the voice.

We have, therefore in this case not a chronic laryngitis, which is a mucosal inflammation, but a muscular disability. This disability is called *myasthenia laryngis*. Parenthetically it should be stated that this has nothing to do with *myasthenia gravis*, which as you know, is a bulbar trouble. The disease in this patient is local and concerns only the laryngeal musculature.

Comment—The cause of this patient's ailment is vocal abuse. On questioning him about his daily life in his best professional days we discover the same things that ruin the voices of most professional singers. They give their larynges no rest. When not singing or rehearsing they are talking constantly. In all their singing they are striving to increase their range upward. They try to overcome the gradually and progressively increasing failure of their voices by increased vocal exercises and change of method, instead of by prolonged intervals of absolute silence.

What can we do for this man's *myasthenia laryngis*? Very little. He can never again regain a voice fit for public performance. He can recover a vocal control sufficient for entertaining a few friends in a living room. He had better try some other occupation possibly teaching. Perhaps he is not too old to acquire ability in instrumental music.

The chief reason for presenting this case is to point out how such sad and numerous cases of breakdown in a musical career can be *prevented*. Singers should be taught that there is a limit to what any human larynx can stand without permanent impairment of those exquisite qualities that make a career in vocal music possible. They should be taught that they must not talk all the time they are not singing. In other words on the days when they must sing in public they should limit their vocal exercises and should be absolutely silent as to conversation. These intervals of silence will go a long way toward preventing strain and fatigue and ruin of the laryngeal muscles.

There is one other factor in many instances of wrecked careers of concert and operatic singers and that is *alcohol* as a beverage. Total abstinence is essential for preservation of those highest qualities of voice that make a vocal career possible.

#### RIGHT LARYNGEAL PARALYSIS DUE TO A SMALL TUMOR LIKE MASS INVOLVING THE RIGHT TRACHEAL WALL, PROBABLY DUE TO TARDIVE GENITAL SYPHILIS

CASE V—Here we have an example of disease of the trachea that is of interest to every practitioner of medicine. This orphan girl is twelve years old. Her voice is not bad, yet she has a paralyzed vocal cord. She has a misleading history. The grandmother states the child has had a chronic cough off and on, all her life; that it was never severe and would often disappear for weeks at a time. A month or

two ago the cough became what the grandmother calls "wheezy" She never noticed that the cough was loose nor that any secretions were brought up

About a week ago the child developed what the grandmother thought was, as she expressed it, "a cold in the throat," for which treatment was sought in the Out-patient Clinic

Mirror examination, done for the first time in this child's life, showed the right vocal cord to be motionless, but the left cord on phonation came across the midline to meet the motionless cord and produced a loud though rough voice

A working diagnosis of paralysis of the right vocal cord was made and the child was referred to the Bronchoscopic Clinic for further study

On examination with the laryngoscope the working diagnosis of paralysis of the right cord and the compensatory adjustment of the left cord were corroborated Passing the laryngoscope through the glottis, a good view of the trachea was obtained About half the lumen was obstructed by a dark red mass projecting from the right side, the upper edge obliterating the fourth ring The mass was pulsating but the pulsations seemed transmitted rather than expansile

To have taken a specimen of tissue with tissue forceps through the laryngoscope would have been quite easy, but we did not do so because the lesion, though it could have been a chondroma, had rather the appearance of a chronic inflammatory condition and the obliteration of the rings suggested perichondritis, which is often due to syphilis The laryngoscope was withdrawn

Palpation of the neck was negative for nodes but palpation of the tracheal cartilages yielded important findings Deep down behind the clavicle on the right side, the rings merged into a small tumor-like thickening that was probably integral with the trachea, on swallowing, the trachea and the thickening moved up and down together Pulsations could be felt but the sensation they gave to the examining finger was that of transmission rather than of expansion

General and roentgen-ray examinations of the child revealed no stigmata or other significant findings Both parents had died by accident, so the question of syphilitic parentage could not be determined The serologic test was negative but had not yet been repeated

Three successive serologic tests were then made The first one was doubtful, the second and third were both positive (1 plus) These if supported by a clear history of parental syphilis, or a history of the presence of other typical lesions, would have established a positive diagnosis of congenital syphilis, but here there was no such supportive evidence.

Under such circumstances a therapeutic test is desirable, but all syphilologists of today wisely agree that it is, as a rule, inadvisable to give spirocheticides until a diagnosis of syphilis has been definitely made However, we felt justified in taking the responsibility of having a test made in this case because the appearance, location and tenderness of the lesion were characteristic of chronic perichondritis, and chronic localized perichondritis in this region is almost invariably syphilitic Moreover, delay was dangerous Suppuration, though not certain to follow a chronic hyperplastic tracheal perichondritis of this type, as it is in acute perichondritis, is always a serious matter in this location, because of the probability of mediastinitis and mediastinal abscess as a sequelae

We therefore supplemented the working diagnosis by making it *right laryngeal paralysis due to a small tumor-like mass involving the right tracheal wall, probably due to tardive congenital syphilis* Our colleagues in the Department of Syphilology concurred in our opinion and took charge of the case They administered neoarsphenamine intravenously starting with a dosage of 0.3 gm (5 grains) The result established the diagnosis of congenital syphilis The Wassermann test rose to 2 plus and later became doubtful After twelve weeks of the

neoarsphenamine treatment the tumor like swelling has flattened out and the tracheal rings have reappeared.

**Comment**—Some of the presented and many of the omitted features of this case are so well recognized and understood that comment may be limited to those features that are often overlooked

1 Palpation of the larynx and trachea is an important diagnostic procedure Palpatory search in the neck for nodes is routine, but the value of palpation of the laryngeal and tracheal cartilages is often overlooked.

2 A patient can have a good voice yet have a paralyzed vocal cord, even both cords may be paralyzed In most of such cases the voice is hoarse at the onset of the paralysis, but readjustment in time usually restores a good voice notwithstanding the fact that the paralysis is permanent The voice may be good with both cords paralyzed and the patient verging on asphyxia.

3 This child had a tumor-like mass of syphilitic perichondritis that pressed upon the right inferior laryngeal nerve, producing a paralysis of the right vocal cord In this connection it is well to recall that there are many different ways in which syphilis may produce hoarseness For example, there may be a gumma, abscess or ulcer in the larynx mechanically interfering with the cords More frequently the lesion is in the central nervous system, a meningitis, a gumma or a tabetic sclerosis, causing a paralysis of the vocal cords Most often the syphilitic cordal paralysis is due to compression of the recurrent nerve by an aneurysm, by lymph nodes a gumma, or as in this case, by a syphilitic tracheal perichondritis Though the symptoms may be entirely laryngeal, the causative syphilitic lesion may be in the brain the neck, or the chest.

As to *prognosis* of the laryngeal paralysis in this child, we may say positively that the paralyzed cord will never move again, no matter what treatment is used but this will not prevent the patient having a good voice because of the adjustment that has been made in cordal approximation

# CHRONIC DISEASES OF THE NOSE, THROAT AND EAR

CLYDE A. HEATLY, M D , F A C S \*

## CHRONIC SINUSITIS

THE most common as well as the most difficult problems encountered in chronic nasal disturbances involve diseases of the nasal sinuses. Many significant advances have been made in recent years in the diagnosis and management of these disorders. The competent rhinologist has learned the importance of allergy in relation to chronic sinusitis from accumulated failures in cases in which this factor had been overlooked. He has also come to a better understanding of the physiology of the nose and thereby to a sounder appreciation of the value of carefully planned surgery which conserves rather than needlessly destroys nasal structures.

**Classification of Sinusitis**—Many classifications of chronic sinusitis have been suggested. It is perhaps simplest from the clinical standpoint to consider three groups: (1) chronic suppurative sinusitis, (2) chronic hyperplastic sinusitis, which is predominantly allergic, and (3) mixed forms in which a chronic infection has been superimposed on an underlying allergy. Allergy produces profound changes in the nasal and sinusal mucosa ranging from simple pallor and edema to extensive polypoid formation. These structural changes favor the stagnation of secretions by interference with ventilation and drainage and thereby promote the chronicity of secondary infections. It is now generally recognized that nasal polyps are a manifestation of chronic nasal allergy in most instances. Their well known tendency to recur, therefore, can be controlled only by appropriate management of allergy.

**Diagnosis**—1 A careful *history* is essential and should include questions directed to a possible underlying allergy. A family history of allergy is of great importance. The studies of Cooke and Vanderveer showed that, considering patients of all ages, about 60 per cent are sensitive with a unilateral family history and 67.5 per cent with a bilateral inheritance. In a group of 220 adult patients with nasal allergy reported by Hansel, 61.4 per cent gave a positive family history.

2 The *intranasal examination* should note the color of the mucous membranes (pale, water-logged, boggy tissues suggest allergy), the presence of septal deviations or polyps, and the position of purulent secretions with relation to the middle turbinate. It will be recalled in

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From the Division of Otolaryngology, Department of Surgery, University of Rochester, School of Medicine and Dentistry, Rochester, New York.

\* Associate Professor of Surgery, in Charge of Otolaryngology and Bronchoscopy, University of Rochester, School of Medicine and Dentistry, Otolaryngology, Rochester Municipal and Strong Memorial Hospitals.

this connection that the anterior group of sinuses (antra, frontals and anterior ethmoids) empty into the nose beneath the middle turbinate, while the posterior group (posterior ethmoids and sphenoids) drain above the posterior portion of this structure. The routine use of the nasopharyngoscope should be urged as part of this study.

3 The *transillumination test* is easily done by any physician and is of particular value in detecting changes in the maxillary sinuses.

4 *Study and culture of the nasal and sinus secretions*. Smears of the nasal secretions and sinus washings should be stained with eosin-methylene blue and studied for eosinophils. In the allergic nose free from infection a preponderance of eosinophilic cells may be demonstrated. In the presence of infection, however, these may be largely replaced by neutrophilic (acute infection) or lymphocytic (chronic infection) cells. In such cases it may be necessary to repeat the nasal smears carefully for several days before eosinophils are discovered. Hansel has repeatedly stressed the diagnostic value of the cytologic examination and it is now accepted as an important part of the study of these chronic nasal and sinus disturbances. The predominating organisms should also be learned by appropriate bacteriological examination.

5 *X-ray examination*. The correlation of well taken radiographs with the clinical and laboratory findings is of the greatest value in chronic sinusitis and should be done routinely in all difficult cases. This study may be further aided by the use of radiopaque substances introduced into the sinuses by cannula or by the displacement method.

*Treatment*—The limits of this paper do not permit a detailed summary of this important subject. This may be just as well since few experienced rhinologists are in complete agreement on many of the technical problems of management. A few general remarks, however, may be permitted.

1 Systemic factors involving general health, constitutional diseases and, in particular, allergic states must be appropriately controlled so far as possible. Remember that the allergic types of chronic sinusitis can never be controlled by local or surgical methods alone, and that many of our outstanding failures spring from a lack of appreciation of this fact.

2 Local mechanical factors which interfere with proper sinus drainage must be surgically corrected. These include deviations of the nasal septum, hypertrophied turbinates and polyps.

3 A period of conservative local treatment including irrigation of the affected sinuses or use of the Proetz displacement technic will cure many of the mild types of infection and is indicated in those cases where preliminary allergic study and treatment is to be carried out. The local use of sulfonamide solutions has not been of striking value in these chronic cases.

4 When it is at once or subsequently apparent that surgical mea-

ures are necessary for cure, *plan* the type of surgery to be tried whenever possible with careful thought to the restoration of a functioning nose. This may involve surgery for ventilation, surgery for drainage, or radical measures for the eradication of hopelessly diseased tissue. Proetz's dictum is worth repeating—"More surgery is almost never an improvement on too much surgery done before."

5 The exact limitations of intranasal and radical sinus surgery are controversial. For example, many experienced rhinologists will advise an intranasal window resection in cases in which others will feel that only radical antrum surgery will suffice. Careful consideration of all the clinical and x-ray findings in the *individual* problem is imperative.

6 Do not be too hasty in advising sinus surgery in asthmatic states. Although the literature contains many reports of striking improvement in asthmatics after radical sinus surgery, there is increasing evidence that such benefit is either temporary or limited to a small group of patients. It is my opinion that sinus surgery in asthmatics should be carried out only after a preliminary period of careful allergy management, and then only when there are pathologic changes in the sinuses that require operation on their own merits or where there is strong evidence of a causal bacterial relation.

#### CHRONIC TONSILLITIS

**Pathology**—The lymphoid structures of the throat include the adenoid tissue in the nasopharynx, the palatine tonsils, the lingual tonsils and scattered, irregularly developed masses on the lateral and posterior walls of the pharynx. All are similar in that they contain lymphoid tissue with germinal centers. The tonsils possess a well defined capsule which facilitates complete and permanent removal by proper surgical methods. The adenoids, however, are loosely formed without encapsulation so that recurrence after removal is commonly observed, particularly in early childhood when a strong tendency to compensatory hypertrophy exists.

A clear understanding of the histologic structure of these tissues is necessary to a proper appreciation of the many disturbances caused by chronic infection. The principal point of interest in this respect lies in the structure of the crypts. These are particularly well developed in the palatine tonsils where they are narrow, deep and ramified in contradistinction to the wide-mouthed, superficial and short crypts seen in the other lymphatic structures of the throat. The epithelium lining these crypts, notably in the palatine tonsils, contains a rich network of capillaries. We know from microscopic study that chronic infection results in ulceration and destruction of portions of this lining epithelium, thus producing a thrombosis of innumerable capillaries as well as many of the larger collecting veins which lie just under the epithelium. The mouths of such infected crypts are frequently closed

by the formation of scar tissue, thus intensifying the infection through lack of drainage. There are no mucous glands in these crypts to assist in the expulsion of bacteria and debris. The possibilities for dissemination of infection are further enhanced by the constant movements of the throat as well as by the compression incident to swallowing. It has been estimated that 75 per cent of all primary foci of infection occur in the mucous membranes of the head. The high incidence of chronic tonsillitis in this group can be easily understood in the light of these considerations.

There has been a decided tendency recently to discount the value of *tonsillectomy* and in fact to consider the whole relationship of focal infections greatly overemphasized. This can prove a healthy point of view if it prevents or even lessens indiscriminate surgery. The importance of the properly indicated and carefully performed tonsillectomy, however, is too thoroughly established to justify a hasty endorsement of this trend.

**The Relation of Chronic Tonsillitis to Certain Systemic Diseases—1**  
*Acute Glomerulonephritis*—From the standpoint of etiology, two important clinical facts must be emphasized. (a) In a great majority of instances acute nephritis follows infections of the upper respiratory tract. (b) Careful bacteriologic and immunologic studies indicate that the hemolytic streptococcus is the chief offender. The removal of diseased tonsils is of great importance in many of these cases. The time for operation should be determined by the internist and is as a rule after the general manifestations of the nephritis have disappeared. Acute exacerbations frequently follow such surgery, but usually subside within a short period.

**2** *Acute Rheumatic Fever*—Rheumatic fever in well over 50 per cent of cases is preceded by a sore throat or tonsillitis. Accumulated experience on the effects of tonsillectomy in this disease may be briefly summarized as follows. (a) It occurs from 25 to 35 per cent less often in tonsillectomized children. (b) When a rheumatic infection has once manifested itself, however, tonsillectomy does not safeguard the child against recurrent attacks nor against carditis.

**3** *Arthritis*—Certain forms of arthritis, notably of the infectious or rheumatoid group, seem to be definitely associated with focal infection and are often promptly relieved when the focus is removed. Needless removal of questionable foci should be avoided, especially in the hypertrophic or degenerative groups.

**4** *Allergy*—It is generally agreed that tonsillectomy does not aid in improving the effects of treatment of respiratory allergy in most instances. Statistics show that nasal or pulmonary allergy may occur with the same incidence in the tonsillectomized and nontonsillectomized groups. When tonsillectomy is indicated it is particularly important to avoid the stage of active allergic symptoms. Patients who

are allergic or who give a positive family history of allergy should not be operated on during the hay fever season because of the danger of inducing bronchial or nasal allergy. Finally, all cases of allergy should be under control before resorting to surgery.

5 *Polihomyelitis*—Evidence has accumulated suggesting that there is a causal relationship between the removal of tonsils and the onset of bulbar polihomyelitis within the time interval corresponding to the incubation period of the disease. While this connection cannot be considered established at the present time in view of the conflicting opinions of competent observers, it would nevertheless seem prudent to avoid tonsillectomy when this disease is prevalent.

### THE CHRONIC EAR

The chronic ear is often bred of neglect and fostered by it. Recent advances in the management of acute aural infections by the intelligent use of chemotherapy may be expected to reduce the incidence of chronic suppuration. It must be emphasized, however, that certain cases of acute otitis, especially those complicating scarlet fever, measles, diphtheria and tuberculosis, have strong chronic tendencies from the onset due to their necrotizing effects on the drum and mucous membranes of the middle ear, as well as to the early bone involvement which frequently follows. The attention of both the physician and the patient is often centered on the mere nuisance of the chronic otorrhea without any thoughtful consideration of the potentially serious complications which may develop. The certain progressive loss of hearing, the possibilities of systemic disturbances from a chronic focus, and finally the constant menace of a sudden serious or fatal intracranial invasion make imperative a careful study of the individual case rather than the routine employment of antiseptic drops and a defeatist attitude.

1. *The Location and Significance of the Perforation*—Two general groups of perforations occur, the central and the marginal. The most meticulous cleansing of the external canal and drum may be necessary to establish this important distinction. The *central perforation* occurs in the membrana tensa and, as the name implies, does not involve the margins of the drum. It is frequently seen in the lower anterior quadrant of the drum as the result of a chronic tubotympanic infection. A large kidney-shaped perforation occupying the lower half of the drum is another common variety. A central perforation is rarely accompanied by necrosis of the bony walls of the tympanic cavity or of the ossicles, and may be properly classified as the *nondangerous form* of chronic otitis.

The *marginal perforation*, on the other hand, must be viewed as an indication of a potentially *dangerous form* of aural suppuration. This type of perforation may appear in variable form, size and location.



but, by definition, shows destruction of the periphery of the drum and the annulus tympanicus. A particularly dangerous form of marginal perforation occurs in the *membrana flaccida* (Shrapnell's area) and is commonly referred to as an *attic* perforation. Perforations of this type may be small, concealed by a dry adherent crust, and easily overlooked by a casual inspection of the drum. They must be considered the most dangerous type of drum perforations because they indicate suppuration of the attic and tympanic antrum, caries of the incus, and a strong probability of cholesteatomatous formation. Total loss of the *membrana tensa* or drum proper should be considered as marginal perforations.

2 **Cholesteatoma**—The formation of cholesteatoma occurs in approximately one third of all chronic infections of the ear. Primary cholesteatoma is rare. The so-called secondary or common type follows perforations of the marginal or attic variety—never central perforations. It is caused by an extension of the squamous epithelium of the external canal and tympanic membrane into the middle ear and as such represents a reparative attempt by nature to cure the suppuration. The cholesteatoma consists of a matrix attached to the bony walls of the tympanic antrum or attic from which masses of squamous epithelium are cast off. The layers of epithelium accumulate and the desquamated masses of epithelial cells are trapped within the bony confines of the tympanic spaces so that a gradually expanding type of tumor is produced. As a result, pressure erosion of surrounding bony structures takes place and invasion of the facial nerve, labyrinth (especially by way of the exposed horizontal canal), or adjacent dural surfaces frequently follows. Such serious complications commonly occur as the result of an acute exacerbation of the chronic suppuration during an acute upper respiratory infection or following swimming.

The cholesteatoma grossly may present a smooth, glistening appearance or in septic cases may resemble a mass of putty. Its odor is characteristically foul. On microscopic study it is found to consist of masses of desquamated epidermis and cholesterol crystals caused by the decomposition of organic matter in the absence of oxygen. In examining a case for the presence of cholesteatoma, material may be secured for microscopic study by passing a small bent cotton applicator through the perforation into the attic region or by gently douching with 50 per cent alcohol through a slender attic cannula. Greasy, foul scales resembling onion skin will be observed floating on the surface of the returned solution. It must be emphasized that many cases of cholesteatoma may remain relatively dormant for many years, with scanty or completely overlooked aural discharge. Such cases are particularly dangerous because the presence of this serious complication is frequently unsuspected until sudden manifest evidences of extension

arise The formation of cholesteatoma may be small, limited to the middle ear or attic, or be of enormous size, destroying and occupying most of the mastoid process

**3 Aural Granulations and Polyps**—Granulations are commonly encountered in all forms of chronic otitis and may arise from any portion of the tympanum or attic They consist of soft, red, easily bleeding tissue and as such are readily identified Polyps may arise from the infected mucous membranes or from granulation tissue itself They vary greatly in size and appearance Many cases are seen in which a large polyp fills the entire external auditory canal It is important to emphasize that, while polyps may arise from the ossicles, edges of the drum or any portion of the bony wall, they are commonly attached to the wall of the labyrinth itself In such instances, removal may precipitate a sudden, overwhelming labyrinthine infection with rapidly fatal meningitis

*It is important to counsel the practitioner against careless removal of aural polyps* If removal is attempted, the base of the polyp should always be cut through clearly with the aural snare, exercising great care to avoid traction In cases of acute exacerbation of a chronic infection with headache, slight vertigo and obstruction to drainage by a large polyp of the canal, the situation calls for immediate radical mastoidectomy, and the physician who attempts to improve drainage by removal of the polyp alone risks a serious complication It is imperative to conduct careful preliminary studies of labyrinthine function in all cases of aural polyps

**4 X-ray Studies**—It is important to obtain complete x-ray studies in all cases of chronic aural suppuration of the so-called dangerous variety Nevertheless, it should be pointed out to the practitioner that such studies are seldom as informative as in acute conditions, usually showing a generalized sclerosis in a poorly developed or infantile type of mastoid Occasionally, however, areas of erosion may be identified, especially in cases of cholesteatoma X-rays should be routinely obtained before undertaking radical mastoid surgery

**5 Treatment—Nondangerous Chronic Otitis**—Chronic infections involving the sinuses or lymphoid structures of the throat must be cleared In selected cases, particularly in childhood, the direct application of radium to the eustachian orifices has proved of value Careful systematic cleansing of the tympanic cavity followed by insufflation of antiseptic powders, such as boric-iodine (Sulzberger formula) or sulfonamide mixtures, is indicated Irrigation of the attic by means of a suitable cannula is an effective procedure especially where the perforation is large or in the upper posterior portion of the drum Alcohol in 50 per cent solution is suitable for this purpose Antiseptic drops such as alcohol (50 per cent) or boric acid (20 grains) in alcohol may be prescribed for home use

*Dangerous Type of Chronic Otitis*—These cases are as a rule best managed by appropriate surgical measures. This is particularly true in the presence of a complicating cholesteatoma. The radical or modified radical operation is generally necessary. The attention of the surgeon should not be distracted by efforts to conserve the already impaired hearing in these dangerous infections. His primary consideration should be meticulous complete removal of the infection. Many of the failures after surgery result from a disregard of this important principle. As a matter of record it should be noted that the hearing may be slightly improved as well as decreased, in about equal proportions after radical surgery.

#### THE TREATMENT OF DEAFNESS IN CHILDHOOD BY IRRADIATION

Most physicians are aware of the fact that enlarged adenoids are at the root of the majority of ear disorders in childhood. The consequent partial or complete blockage of the eustachian orifices frequently results in an insidious slowly progressing deafness recurring attacks of acute middle ear suppuration or a persistent chronic otorrhea of the nondangerous variety. It is not so commonly realized that recurrence is exceedingly common after adenoidectomy before the age of puberty (in fully 75 per cent of cases according to Crowe) and that this recurrence or compensatory growth is frequently around the eustachian orifices where complete surgical removal is difficult or impossible because of possible damage to those important structures. The resulting tubal obstruction over a period of time causes disturbances in the mucous membrane of the middle ear, varying from early hyperemia and secretory changes to the formation of a myxomatous or fibrous tissue which interferes with the mobility of the ossicles.

While the physician may suspect a hearing disturbance from otoscopic evidence of retraction of Shrapnell's membrane or of the entire drum, only careful audiometric studies will show its true proportions. The earliest changes are in the high tones between 10 000 and 16 000 double vibrations, which are far above the speech range but as the mucous membrane changes progress the tones within the speech range gradually become involved. This impaired hearing for high tones with good hearing for low tones is the earliest symptom of middle ear deafness in childhood. Although apparently contrary to the classical dictum in otology that such high tone loss indicates an inner ear or nerve lesion the extensive investigations of Crowe and his associates have established it as a clinical fact.

The possibilities of reducing the size of lymphoid tissue and temporarily inhibiting its growth by irradiation in doses too small to injure surrounding structures have been known for many years. Crowe and Burnham first made extensive clinical use of radon applied by means of a special applicator passed through the nose to the region of the

eustachian orifices. Their success in so treating these cases of middle ear deafness in childhood has prompted others to employ a similar method, using radium rather than radon.

The writer and his associates in 1942 reported\* on the successful use of a special applicator holding two 12.5 mg. radium needles in its head. The use of two such applicators, using a total of 50 mg. of radium, permits the treatment of both eustachian orifices in twelve minutes, delivering a dose of 5 milligram hours to each orifice. Such a short treatment time with this small amount of radium is made possible by the fact that a high proportion of beta radiation is used in actual contact with the area to be treated. The applicators are small and can be introduced in most children under local anesthesia. An interval of three months is usually allowed before a second irradiation is given. This dosage is far below the amount of radium which could cause any injury to the mucous membranes and surrounding structures. The results have fully substantiated the successes reported by Crowe and his associates. The physician who is alert to the frequency of deafness in childhood and its common cause may thus render a valuable service in preventing the establishment of permanent changes.

\* Emerson, E. B., Dowdy, A. H., and Heatly, C. A. Use of Radium in Treatment of Deafness by Irradiation. *Arch. Otolaryng.*, 35: 845-852 (June) 1942.

# THE TREATMENT OF BRONCHIAL ASTHMA AND OTHER CHRONIC PULMONARY DISEASES ACCOMPANIED BY CONSTRICTION IN THE BRONCHIAL PASSAGEWAY

ALVAN L. BARACH, M.D., F.A.C.P.\*

THE treatment of bronchial asthma is generally presented from two points of view (1) investigation of the allergic factor through the use of the skin test work-up, elimination diets and removal of or desensitization against the offending substance, and (2) palliative treatment, including drugs which produce temporary relief of bronchial spasm, such as epinephrine and aminophylline. Despite this combined therapeutic endeavor, many patients with bronchial asthma suffer from recurrent and more or less severe bronchial spasm. In some instances, pulmonary overdistention is followed by varying degrees of invalidism or by emphysema of the lungs.

The purpose of this clinic is to present a method of treatment that is based neither on the allergic nor palliative approach but rather on an understanding of the pathological physiology of bronchial spasm as it affects the lungs and mucous membrane of the small bronchioles. The principle involved in this physiologically directed therapy may be described as "repeated bronchial relaxation."<sup>1</sup> The administration of adrenalin produces a temporary relief from bronchial spasm, but repeated injection is not followed by a progressive relaxation of the bronchial spastic muscle. On the contrary, the patient with asthma frequently becomes less and less responsive to epinephrine, either by injection or by inhalation, and a state of intractable asthma or even status asthmaticus may take place.

In using the phrase "repeated bronchial relaxation," I refer to a cumulative relaxation of the circular muscle that surrounds the intrathoracic bronchi and bronchioles, which ultimately results in a continuously patent passageway into the lungs, i.e., a remission of the symptoms of asthma. Although this principle of treatment first became apparent as a consequence of intermittent inhalations of helium-oxygen mixtures, repeated bronchial relaxation may now be more simply obtained in many cases without the use of helium therapy. In patients who do not respond satisfactorily to the simplified program of bronchial relaxation, the inhalation of helium with oxygen may be necessary to secure a good remission from the symptoms of the disease.

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From the Department of Medicine, College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York City.

\* Associate Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University; Assistant Attending Physician, Presbyterian Hospital.

Following the discussion of the pathological physiology of severe asthma, I will, therefore, outline a program that may be carried out in the absence of helium-oxygen therapy, and one that includes the administration of this lighter-than-air gas where facilities for its effective administration are present. Either regimen may be carried out in the hospital, home or office, although the administration of helium by hood is more practical in a hospital with trained personnel.

#### PATHOLOGICAL PHYSIOLOGY OF OBSTRUCTIVE DYSPNEA

An understanding of the disturbed mechanics of respiration in obstructive dyspnea will be of help in carrying out therapeutic procedures which are based on the physiological state of severe asthma. When an obstruction is experimentally produced in an animal by decreasing the diameter of the larynx to one-third the normal lumen, the first effect observed is the increased effort on the part of the respiratory musculature to draw air into the lungs. Measurement of the intrapleural pressure reveals an immediate increase in negative pressure during the act of inspiration, in expiration the intrapleural pressure approaches the atmospheric pressure. The consequences of obstruction during inspiration can be separated from the effects of obstruction during expiration. When inspiration is allowed to proceed normally but expiration is conducted through a constricted orifice, an increased effort on the part of the animal is observed during expiration, accompanied by a change in intrapleural pressure toward that of the atmosphere during the expiratory cycle. The intrapleural pressure during inspiration is unchanged, and at the end of five hours a dog shows no progressive increase in dyspnea.

When expiration is allowed to proceed normally but inspiration is conducted through a constricted orifice, however, a progressive increase in negative intrapleural pressure takes place during the inspiratory cycle. This is accompanied by more and more severe dyspnea, edema of the lungs and death of the animal. Although autopsy of dogs who exhaled against a localized obstruction (or positive pressure) showed little or no change in the lungs as long as inspiration was allowed to proceed normally, the pathological anatomy of animals subjected to resistance during inspiration (or comparable negative pressures) was that of pulmonary congestion and edema, more marked in the dependent portions of the lung, with areas of emphysema at the periphery.<sup>2,3,4</sup> We are, therefore, confronted with the basic pathophysiological factor in obstructive dyspnea, namely, that elevated negative pressures within the chest during the inspiration result in extensive damage to the lungs. The mucous membrane of the medium and small intrathoracic bronchi are likewise exposed to a negative pressure which exerts a cupping action on them, resulting in congestion and edema, as well as increased formation of mucus. This

swelling of the mucous membrane, as well as the production of increased expectoration, increases the degree of obstruction and affords an explanation for the fact that bronchodilatory drugs may not always result in prompt disappearance of the symptoms of obstructive dyspnea.

An additional consequence of the elevated negative intrapulmonary pressure is to increase the inlet of blood into the right heart but retard the exit of blood from the lungs. During expiration against resistance, the flow of blood into the right auricle is accomplished by a compensatory rise in systemic venous and arterial pressures. If expiratory obstruction is so severe as to result in a marked increase in intrapulmonary pressure, the total cardiac output may be decreased. The preponderant effect of obstructive dyspnea in both cycles of respiration is that of congestion and edema, both in the alveoli and in the mucous membrane of the smaller bronchi. This is due to the pathologically elevated negative pressure in the lungs during inspiration although opposed by the relative increase in positive pressure during expiration.

When obstructive dyspnea is due to constriction in the extrathoracic trachea or larynx, inspiration and expiration are approximately equally prolonged. The instantaneous increase in pulmonary ventilation is stimulated by proprioceptive reflexes in the lungs. Dyspnea is then aggravated by accumulation of carbon dioxide and anoxia due to pulmonary congestion, edema and irregular incomplete ventilation of the alveoli, which impairs diffusion of oxygen into the blood. In the early stages of obstructive dyspnea, increased ventilation may result in a blowing off of carbon dioxide with a slight shift in pH toward the alkaline side but as pathological changes occur in the lungs the efficiency of carbon dioxide elimination is impaired and carbon dioxide retention may be accompanied by an alteration in acid base equilibrium toward the acid side. It must be borne in mind, however, that an elevated carbon dioxide content in the arterial blood and the alveolar air makes possible a larger excretion of carbon dioxide per unit volume of breathing, which tends to retard the development of an uncompensated acidosis.

When obstruction takes place within the chest, expiration is prolonged, due to the fact that intrathoracic bronchi enlarge during inspiration and constrict during expiration. Under these circumstances, a forcible inspiration will result in the passage of air through an area of bronchial narrowing into the alveoli the walls of which are subjected to an increased negative pressure. During expiration the volume of the chest is diminished and the bronchioles are constricted so as to hinder the exit of air from the alveoli. The succeeding inspiration draws additional air into the distended alveoli and further pressure is placed on the thinned-out walls, resulting in impairment of capillary

circulation and at times in rupture of the wall. The duration of expiration in patients with asthma (or obliterative bronchiolitis) may be two to three times longer than inspiration, since an approximately equal volume of air is delivered through tubes that are about 30 per cent smaller in diameter during the expiratory cycle and because inspiration is achieved by the employment of higher pressures than expiration. Acute attacks of dyspnea, brought on either by bronchial spasm or exercise, may result in a temporary overdilatation of the lung alveoli because of this impaired mechanism of emptying. Although the intrathoracic bronchial passageway in normal individuals shows an increased diameter during inspiration and narrowing during expiration, the degree of expiratory bronchial constriction in patients with asthma may be very marked, as has been observed during bronchoscopic examination. The use of positive pressure in inhalational therapy has the advantage of maintaining a more patent lumen during expiration,<sup>5</sup> as well as combating pulmonary edema<sup>4</sup> and decreasing inspiratory dyspnea.<sup>6</sup>

The use of helium was introduced by the author for the treatment of obstructive dyspnea only.<sup>7, 8, 9</sup> During quiet breathing the substitution of helium for nitrogen results in no change in the effort of respiration. Since, however, the velocity of movement of a gas through a constricted orifice is inversely proportional to the square root of the density of the gas, the pressure required for the movement of an 80 per cent helium 20 per cent oxygen mixture past the point of localized obstruction is almost one-half that required to breathe oxygen or air. If the constriction in a tube were to be continued in a linear direction, no decrease in pressure would be manifested when a helium-oxygen mixture was substituted for air, since the viscosity of helium is, in fact, slightly higher than nitrogen. In urgent dyspnea, however, even without localized obstruction, a smaller pressure will yield a larger pulmonary ventilation when helium-oxygen mixture is substituted for air. During the inhalation of a helium-oxygen mixture in patients with respiratory obstruction, the negative pressure during inspiration is diminished by the inhalation of 80 per cent helium with 20 per cent oxygen. Furthermore, a swifter and more complete emptying of the lung air has been shown when the helium-oxygen mixture was inhaled. In many instances the volume of breathing in the presence of wheezing respiration is diminished 25 per cent when 80 per cent helium with 20 per cent oxygen is substituted for either air or pure oxygen.

#### CLINICAL RESULTS OF HELIUM-OXYGEN THERAPY

When helium-oxygen therapy was first used in the treatment of status asthmaticus, the inhalation of this lighter-than-air gas was kept up for a period of two to five days. In other patients with intractable asthmas, inhalation of helium with oxygen was conducted for two



hours twice a day. It was soon observed that the majority of patients treated in this way were relieved of asthma for a considerable period of time thereafter. In a series of eighty-four previously reported cases of status asthmaticus and intractable asthma, inhalation of helium-oxygen mixtures was followed by complete freedom from asthma or exceedingly mild asthma in forty instances, in thirty-six cases a marked alleviation of the symptoms of asthma took place with the restoration of sensitiveness to adrenalin, in the remaining eight cases improvement was either very slight or transient. In thirty patients in this series in whom follow-up observations could be made, fifteen maintained either all or a substantial part of their improvement for six months or more.<sup>10 11</sup>

The mechanism of improvement was traced in part to the local relaxation which repeated inhalation of the helium-oxygen mixture produced, in addition, the mucous membrane in the bronchioles was not exposed to the pathologically elevated negative pressure during the inspiratory cycle, which tended to diminish the congestion, edema and the production of mucus, which was previously shown to be produced by a maintained negative intrapulmonary pressure. One of the advantages of a less effortful type of breathing appeared to be the general feeling of relaxation induced by alleviation of the dyspnea itself. Additional bronchial relaxation may take place as the result of efferent impulses from the cerebrum.

The value of relieving tension in the central nervous system is shown by the frequent beneficial response to injection of morphine, or preferably dilaudid. Although repeated injection of morphine in the treatment of asthma is unwise, since the drug is habit-forming and because respiratory depression may ensue, the administration of small doses for a limited period is completely justified and often of great value. The point of the present appraisal of the use of dilaudid is to emphasize its usefulness as part of the program of repeated bronchial relaxation, which will be described in detail later.

#### PHYSIOLOGICAL ADVANTAGES OF REPEATED INJECTION OF AMINOPHYLLINE

Since it had been observed that repeated inhalations of helium with oxygen resulted many times in a remission of the symptoms of severe asthma, this principle was extended to the use of aminophylline. In many clinics the effective administration of helium therapy cannot be undertaken because of lack of equipment or trained personnel. The substitution of repeated injection of aminophylline for helium-oxygen inhalation may be carried out in many cases and an excellent clinical result be obtained. A program of combined helium-oxygen inhalation and aminophylline therapy has been previously reported in forty-six hospital patients in whom disappearance of asthma or exceedingly mild asthma, resulted in thirty-four cases with restoration of epineph

rine sensitivity and moderate asthma in nine cases. In fifty-four courses of this type of therapy in ambulatory or office patients, disappearance of asthma, or exceedingly mild asthma, took place in twenty-three instances, with restoration of epinephrine sensitivity with moderate asthma in seventeen cases. The duration of improvement in ninety-one courses of this type of therapy, including both hospital and ambulatory cases, was over one year in fifteen patients, from five to twelve months in twenty, and from one to four months in twenty additional cases.<sup>1</sup>

The demonstration that intravenous injection of aminophylline (theophylline ethylenediamine) was of great value in the treatment of patients who had become refractory to epinephrine should be considered a milestone in the treatment of severe asthma.<sup>12, 13</sup> This drug results in a lowering of venous and intrathecal pressures, dilatation of the coronary artery, stimulation of respiration and an increase in the total volume of blood flowing through the pulmonary circulation.<sup>14</sup> Experiments on the excised lung suggest that the action of aminophylline is directly on the bronchial musculature, since the drug under these conditions also causes a relaxation of the spastically contracted bronchial circular muscle and thus re-establishes the normal diameter of the bronchus.<sup>15</sup>

Since the program of repeated bronchial relaxation calls for administration of aminophylline twice daily for a period of one week and then once daily for a period of one to two months, the intravenous route of administration did not appear practicable. Fortunately, the rectal instillation of 0.6 gm. of aminophylline in 20 cc. of water generally resulted in a degree of relaxation that was almost as complete (although not as prompt) as intravenous injection of 0.48 gm. of the drug.<sup>10</sup> In addition, the dizziness and palpitation at times occurring after intravenous injection do not take place, except very rarely, when rectal instillation is used. Oral administration of aminophylline does not usually terminate severe asthma, although giving the drug by mouth is effective when the symptoms are of mild or moderate intensity. Repeated intramuscular injections are impractical because they produce considerable soreness in the gluteal region. A conspicuous advantage of rectal instillation is that the patient is readily taught to employ the procedure himself at home.

#### IODIDES, GLUCOSE, COLONIC ETHER

We will now mention several other remedies that are useful in the treatment of intractable asthma. In some patients in whom bronchial spasm recurs with considerable severity and frequency, additional relaxation may be accomplished by rectal instillation of 50 to 90 cc. of ether mixed with equal parts of olive oil.<sup>16</sup> At times it is necessary to obtain a degree of relaxation comparable to that required in surgical

anesthesia, and when that is the case the procedure may be carried out under the supervision of an anesthetist. A partial or a complete remission in the symptoms of the disease may result. Other sedative drugs may be employed by rectum, such as paraldehyde, 20 cc. mixed with an equal quantity of olive oil. Both ether and oil and paraldehyde may be repeated two or three times in cases unresponsive to aminophylline therapy. Sedation is aided in apprehensive cases by repeated injection of dilaudid,  $\frac{1}{32}$  grain, at eight- to twelve-hour intervals for two or three days, when oral or rectal use of this drug is insufficiently effective.

In a few cases the development of a slight fever may be followed by bronchial relaxation. This may be conveniently initiated by triple typhoid vaccine administered subcutaneously.

The intravenous injection of 50 cc. of 50 per cent glucose every day or every other day for three or four times has clinically been found helpful in certain cases. An explanation for the good results sometimes obtained by the injection of this hypertonic solution may be the withdrawal from the bronchial mucous membrane of local edema. It is also possible that other effects may be involved, such as a lowering of serum potassium.<sup>17</sup>

Patients with severe asthma appear to be almost uniformly benefited by the administration of potassium iodide, both during the state of continuous wheezing respiration as well as during the intervals between attacks. This drug not only stimulates the flow of mucus from the nose, throat and bronchial mucous membrane, but it seems to possess almost a specific effect in making less likely a recurrence of symptoms.

We have tried residence in filtered air chambers for ten years in the treatment of intractable asthma, with generally disappointing results. The value of filtered air is manifested in those cases in which pollen sensitivity is unquestionably present. In an individual who has hay fever and bronchial asthma the provision of filtered air would provide symptomatic relief by removal of the offending pollen. In some patients in whom intractable asthma has been provoked by pollen the symptoms may persist for a prolonged period of time unless a program of bronchial relaxation is pursued.

#### ADMINISTRATION OF OXYGEN

Administration of oxygen is generally indicated in cases of status asthmaticus, since removal of anoxia may prevent cardiorespiratory failure and decrease the effort of breathing by lowering the pulmonary ventilation. Furthermore, when sedative drugs are used continuous oxygen inhalation overcomes the anoxia which might otherwise be produced by substantial decrease in the volume of breathing. An oxygen tent or a nasal catheter is generally preferable to a face mask since

continuous therapy is more comfortably provided by these methods. If a face mask is employed, a high flow of oxygen, 6 to 10 liters per minute, may be required in the BLB apparatus<sup>18</sup> to prevent the patient from inhaling air through the sponge rubber discs, i.e., to prevent negative pressure developing in the mask. In the Meter mask<sup>19</sup> the mixture of oxygen and air is made by an injector attached to the oxygen tank, which provides a high flow of an air-oxygen mixture with minimal resistance. The meter may be set at 40 to 95 per cent oxygen as required.

In cases of status asthmaticus the patient is placed in 50 or 60 per cent oxygen in a tent, or one of the other simpler methods referred to above is used, in the intervals between helium-oxygen treatment. In the absence of helium therapy the administration of oxygen should be continuous, generally in a concentration of 50 per cent, until the patient is out of danger. We have as yet found no indication for the employment of carbon dioxide in bronchial asthma, although this gas is said to act as an expectorant.<sup>20</sup> However, potassium iodide is from long experience a more dependable drug. In most cases of asthma the expectoration is the result of the negative pressure induced by bronchial spasm, although it often seems to the patient that mucus is the cause of the attack. In many cases, however, an accumulation of mucus during the night takes place and must be expectorated in the morning to provide a clear airway. To accomplish this purpose the inhalation of the nebulized spray of 1:100 epinephrine is the most satisfactory procedure.

#### INHALATION OF 1 PER CENT EPINEPHRINE AND 1 PER CENT NEOSYNEPHRIN

Inhalation of 1:100 adrenalin, produced by a satisfactory nebulizer, has decisive advantages over subcutaneous injection in most patients, since a relatively small amount of the drug is thereby absorbed and systemic effects consequently not produced.\* In patients who have

\* The nebulizer employed in our investigations during the past five years has been that made by the Vaponefrin Company. In this nebulizer the solution is thrown, either by the pressure of the hand bulb or by a stream of oxygen from a cylinder, against a glass baffle plate which breaks up the epinephrine solution into a fine suspension. This can be observed floating in the air for a perceptible interval after it has left the nebulizer and for this reason may be expected to reach the smaller bronchi. The epinephrine employed for nebulization has been that contained in vaponefrin solution, which has been described as racemic methylammonohydroxy-ethyl-dihydroxy-benzene hydrochloride.<sup>21</sup> Vaponefrin solutions have been found more stable than epinephrine solutions when stored under similar conditions, and retain their pressor potency when discolored.<sup>21</sup>

We have observed no irritative effects from the use of vaponefrin solution in moderate amounts over periods of three years. When patients employ the spray excessively, drying of the throat and larynx may take place, but even under these circumstances no lasting harmful effects have been noted. It should be emphasized that use of vaponefrin or epinephrine many times during the day and night is bad practice since progressive refractoriness to the drug is thereby promoted, and

abrupt severe paroxysms, hypodermic administration of adrenalin may at times be necessary until progressive bronchial relaxation has been accomplished. However, it has become apparent from observation of many cases of status asthmaticus that frequently repeated injections of adrenalin lead to a progressively more severe state of bronchial spasm. It should be recognized that, when adrenalin is repeated three to six times a day, the condition of the patient may get worse even in the presence of a program of bronchial relaxation. The reason for this is not clear but the fact that it does take place in certain patients is unquestionable. Secondary vasodilatation of the mucous membrane of the bronchi may be involved. Attempts should, therefore, be made to discontinue hypodermic adrenalin medication at the onset of the regimen of repeated bronchial relaxation, and to employ the inhalation of vaponefrin or epinephrine at such intervals as may be required by acute paroxysms of wheezing or coughing.

#### TECHNIC OF TREATMENT

**Aminophylline**—If aminophylline is prescribed *intravenously* it is better to give 0.48 gm. than 0.24 gm. Since the latter dosage occurs in a 10-cc. ampule, the physician is frequently tempted to employ the smaller dosage. However, much more complete and lasting relaxation will occur when two ampules are used. Dizziness, palpitation and feelings of faintness should be avoided by taking the precaution of administering the solution slowly, i.e., in an eight-minute period.

When aminophylline is given *by rectum* it is highly desirable to follow out the method we have advocated. Powder (or capsules) of the drug should be on hand containing 0.5, 0.6 and 0.7 gm. of aminophylline. For patients in the lower weight classification the smaller dosage 0.5 gm., is employed, for persons of moderate weight, such as 150 pounds a dose of 0.6 gm., and for patients in the neighborhood of 180 pounds or over, 0.7 gm. may be used.\* The powder is placed in a receptacle containing 20 cc. of lukewarm tap water and gently stirred for half a minute. A No. 10 French rubber catheter is thoroughly greased with KY jelly and passed into the rectum for a distance of approximately 3 to 4 inches. The aminophylline solution is then drawn up into a 20-cc. syringe and the solution injected through the catheter. The open end of the catheter has to be cut off so as to make a tight fit between the syringe and the catheter. It is preferable although not necessary for the patient to rest for an hour after the injection. The reason for rehearsing this procedure in detail is that the employment of an enema tube may not only be irritating but is often responsible for

In many patients who weigh between 110 and 150 pounds, 0.7 gm. may be necessary to produce bronchial relaxation, even if nausea and vomiting result.

increasingly severe asthma may result. When attacks of wheezing respiration recur at increasing frequent intervals despite inhalation of adrenalin, a program of bronchial relaxation should be instituted by one of the methods described.

opening up the anus to such an extent as to result in subsequent leakage of the solution into the bed

**Helium-Oxygen Therapy**—When helium-oxygen therapy is administered in a helium hood, a positive pressure of 4 cm of water is generally employed<sup>22 23</sup> The pressure may, however, be varied from 1 to 6 cm, the higher pressures being more effective in terminating inspiratory dyspnea, since the helium-oxygen mixture is gently pushed into the lungs under these circumstances The hood should be used with the new soft rubber collar that has an upward extension around the neck approximately 3 inches long \* A flow of 2 to 3 liters per minute of the helium-oxygen mixture, with 0.5 to 1 liter of oxygen, will maintain a positive pressure if the collar is suitably adjusted Unless a specially trained technician or doctor is available, helium-oxygen therapy cannot be effectively administered in a positive pressure hood

If the Meter mask is employed, the inspiratory valve is removed and a flow of 6 to 8 liters of an 80 per cent helium 20 per cent oxygen mixture is administered, depending upon the weight of the patient and the degree of dyspnea It is desirable to connect the helium-oxygen cylinder with an oxygen tank by a Y tube and administer 1 to 2 liters of oxygen if the patient has pulmonary emphysema, or even functional pulmonary overdistention, either of which is generally manifested by cyanosis † When the regulator is set at a given flow, such as 7 liters per minute, it must be borne in mind that the actual flow when a helium-oxygen mixture is used is 1.7 times the indicated rate These high flows are relied upon to prevent excessive accumulation of carbon dioxide in the large latex bag When the Meter mask is used for helium-oxygen therapy, the meter should either be removed and a water bottle substituted for it, or it should be filled one-third full with tap water to provide adequate humidification If the B L B mask is employed, similar flows of the helium-oxygen mixture are used It should be remembered that the flow of the helium-oxygen mixture is to be maintained sufficiently high to prevent the necessity for drawing air through the sponge rubber disk in the B L B apparatus

#### CHRONIC BRONCHITIS AND OTHER CHRONIC PULMONARY DISEASES ACCOMPANIED BY CONSTRICTION IN THE BRONCHIAL PASSAGEWAY

In many chronic affections of the lungs, such as chronic bronchitis, obliterative bronchiolitis, bronchiectasis, pulmonary emphysema and pulmonary fibrosis, varying degrees of constriction in the respiratory passageway may be present In some cases infection is responsible for inflammatory swelling of the mucous membrane, in others bronchial

\* This may be obtained from the Oxygen Equipment Manufacturing Co., 405 E. 62nd St., New York, N. Y.

† It is frequently more convenient to employ a tank of 25 per cent oxygen 75 per cent helium than to use a separate oxygen and helium-oxygen cylinder

spasm is intermittently found. The principles of bronchial relaxation described above may be utilized in securing a more patent bronchial passageway in these illnesses. Since the clinical entities referred to are chronic in a more continuous sense than bronchial asthma, neosynephrin has the advantage of a drug that does not develop refractoriness, such as may happen with frequently repeated use of adrenalin. Neosynephrin is admittedly a poor bronchodilator but its vasoconstrictive action is more prolonged than that of adrenalin and is not apt to result in secondary vasodilatation. Inhalation of the nebulized spray of 1 per cent neosynephrin two to three times daily is frequently helpful in increasing the patency of the bronchial passageway. Although this may be given by a handbulb it is often preferable for the patient to purchase a regulator and nebulize 0.5 cc. of the 1 per cent neosynephrin solution by means of an oxygen flow of 4 to 5 liters per minute. In this way a more adequate dosage of the drug is obtained, there are no side reactions to this medication. Inhalation of small amounts of epinephrine, or vaponefrin, by handbulb, or 0.25 cc. by oxygen spray, may also be used two or three times daily, frequently with considerable subjective relief of dyspnea. Excessive use of the drug must be guarded against.

In the course of any of the above-mentioned chronic diseases of the lungs, acute infection may usher in a state of intractable bronchial spasm. Under these circumstances all the measures outlined for the treatment of bronchial asthma may be employed. The continuous inhalation of oxygen-enriched atmospheres is of crucial value in acute respiratory insufficiency caused either by infection or overexertion. After one to two or three weeks, the concentration of oxygen should be *gradually* lowered to that of the atmosphere. The nasal catheter is almost essential for a slow reduction in the oxygen percentage of the inhaled atmosphere. This may require two to three weeks. Nasal oxygen may be begun at 5 liters per minute, and the flow diminished 0.5 liters every day. The patient may then develop a remarkable adaptation to a sea level atmosphere, although some dyspnea may persist, especially on exertion.<sup>11</sup> In some patients with pulmonary fibrosis and pulmonary emphysema, the inhalation of 70 per cent oxygen for one-half an hour morning and night may be provided by the Meter mask. This results in a partial and temporary but still useful decrease in pulmonary distention in those cases in which an oxygen debt is present.

Each case of chronic pulmonary disease requires an individual appraisal of the pathological physiology involved in his condition. Chronic infection in the bronchi may be treated by chemotherapy when the organisms that are responsible for the condition have been determined to be those which respond to the sulfonamide drugs or to penicillin. Inhalation of the nebulized spray of sulfadiazine in 2.5 per cent ethanolamine solution has been used but our experience now indicates that it is less effective than oral administration of the drug. The

advantages of obtaining a high local concentration of sulfadiazine in the lung with a low blood concentration justifies its trial in some patients with chronic infection

#### PROGRAM FOR REPEATED BRONCHIAL RELAXATION

Since helium-oxygen therapy is not generally available, two regimens will be outlined, the first without helium therapy and the second including its use

1. Without Helium-Oxygen Therapy—The aim of treatment in both intractable asthma and status asthmaticus is to produce as complete relaxation of the bronchi as possible by the cumulative effect of several procedures. The effect of repeated relaxation is to usher in a state of remission of the symptoms of severe asthma. In patients who are seriously ill with continuous dyspnea and cyanosis, oxygen therapy<sup>\*</sup> is indicated to prevent the consequences of untreated anoxia, especially respiratory failure. In other cases in which repeated injections of adrenalin accomplish temporary and transient relief, oxygen therapy may not be required. Intractable asthma may then be treated either in the home or hospital, or in office practice, utilizing the methods which follow

(a) Rectal instillation of 0.5, 0.6 or 0.7 gm of aminophylline in 20 cc of water is carried out. This procedure is then repeated morning and night for approximately five days, and then continued once at night for three weeks to three months, depending on the severity of the disease. In some patients, aminophylline by rectum is given three times daily.

(b) Inhalation of a spray of 1 per cent epinephrine or vaponefrin is given after the rectal instillation of aminophylline and at four- to eight-hour intervals when wheezing respiration recurs. A hypodermic injection of 0.5 to 1.0 cc of a 1:1000 solution of adrenalin may rarely be necessary at the start of the program but the sooner it is discontinued the better. The epinephrine solution may be nebulized either by means of the handbulb or by an oxygen stream from a cylinder. If an oxygen cylinder is available, 0.5 cc of the drug is nebulized at a flow of 4.5 liters per minute. At the same time, 0.5 cc of 1 per cent neosynephrin is also nebulized. The open end of the nebulizer should be inserted well into the mouth above the tongue with the lips open.

(c) The saturated solution of potassium iodide is administered, 1 cc three times daily for the first week and then 0.3 cc morning and night for an indefinite period. When acne breaks out the drug is stopped until it disappears and then begun again at a dosage of 0.5 cc once daily.\*

\* In some patients with bronchial asthma, excessive formation of mucus may result from prolonged administration of potassium iodide. In these cases the drug should be stopped, since difficulty may be experienced in eliminating too abundant secretions from the bronchi.



(d) Dilaudid is given, preferably by mouth,  $\frac{1}{20}$  grain, once daily for four or five days and then discontinued. For acute severe paroxysms of asthma, hypodermic administration,  $\frac{1}{32}$  grain, may be used at the outset but it is far preferable to utilize this drug either by mouth or dissolved in the aminophylline solution. At times, it is serviceable to give dilaudid by mouth twice a day,  $\frac{1}{20}$  grain, for a period not longer than five days. When dilaudid is discontinued codeine may be prescribed for one to two weeks, 0.03 to 0.06 gm. twice daily.

(e) Intravenous injection of 50 cc. of 50 per cent glucose may be employed if the above program does not manifestly result in marked improvement by the third day. It may be repeated on two following days or on alternate days for two additional times.

(f) If the patient appears to show little improvement as the result of instillation of rectal aminophylline, an intravenous injection in the middle of the day of 0.48 gm. may be given. In some cases the patient may be refractory even to aminophylline. This is more apt to take place in those cases that have had repeated frequent subcutaneous injection of adrenalin.

(g) Rectal instillation of 50 to 90 cc. of ether with an equal amount of olive oil may be given, in patients refractory to this program.

(h) Sedation is generally best obtained with phenobarbital, 0.1 gm. two or three times daily. Seconal or amytal may also be used at night.

2. With Helium Oxygen Therapy.—The above program is used, when helium-oxygen therapy is available, by the addition of the administration of 25 per cent oxygen and 75 per cent helium in a hood under 3 to 6 cm. water positive pressure, two hours twice daily. If the Meter mask is available, in the hospital or at home, the patient is treated with inhalation of an 80 per cent helium 20 per cent oxygen mixture for one hour two or three times daily. In office practice, helium therapy is given for one hour following a rectal injection of aminophylline. In cases which manifest cyanosis, a flow of 1 to 2 liters of oxygen is added to a helium-oxygen flow of 6 to 8 liters per minute. The inspiratory valve is removed in administration of helium-oxygen therapy by mask. Our practice has been to terminate administration of helium after a five-day period but to continue rectal instillation of aminophylline for a period of three weeks to three months, as mentioned above.

In many cases aminophylline by mouth may be advantageously employed on arising in a dosage of 0.2 or 0.3 gm., to prevent wheezing during the day. When rectal administration of the drug is discontinued, oral medication may be substituted, for a prolonged period. Since aminophylline is mentally stimulating the evening dose may cause the patient to be wakeful. If actual insomnia is induced seconal, 0.1 to 0.2 gm., may be required. For patients who still have some residual asthma after a program of bronchial relaxation, aminophylline 0.2 gm., is prescribed after breakfast and on retiring for an indefinite period. Inhala-

tion of the nebulized spray of epinephrine (or vaponefrin) for mild wheezing and coughing, especially on arising, is frequently necessary in chronic cases of bronchial asthma with considerable expectoration. Hypodermic injection of adrenalin is almost always stopped completely.

#### COMMENT AND SUMMARY

The disturbance in the physiology of breathing produced by constriction in the bronchial passageway is the basis for the treatment suggested in this paper. In a number of patients with intractable asthma, specific desensitization therapy has been found ineffective to prevent recurring attacks of bronchial spasm, which is often accompanied by varying degrees of functional pulmonary emphysema. Palliative treatment with adrenalin is of little value, affording temporary or transient relief in the majority of patients. Furthermore, repeated frequent injection of adrenalin is apt to result in a disease manifesting itself by increasingly severe attacks of bronchial spasm.

The principle of repeated bronchial relaxation is not considered as a palliative remedy, since it may usher in a freedom from the symptoms of the disease for periods as long as one to three years. In the majority of cases treated in the manner described, the symptoms of severe asthma have been either absent or mild for approximately seven months. Although recurrence of more severe asthma will take place in many patients, the simplicity of the program is such that the patient may again become free from the condition in its severe and, at times, invalidizing form. In a small percentage of patients, no lasting remission is obtained and attempts to relax bronchial spasm must be maintained. In this group, rest and sedation are required for a prolonged period.

Although the results of repeated relaxation of the bronchiolar circular muscle were first observed as a consequence of helium-oxygen therapy, the use of this principle in the management of patients with severe asthma may now produce similar results in those clinics in which expert provision of helium-oxygen inhalations is not available. The cumulative and summation effect of procedures which result in relaxation of the spastically contracted bronchial muscle is the central theme of this principle of treatment. None of the measures advocated will produce the type of lasting remission which is the aim of this treatment, if administered for a short time only. Intravenous injection of aminophylline is the single, most effective remedy now available for the initial treatment of intractable asthma or status asthmaticus. However, to stop treatment with one or two or three injections of aminophylline because the patient is no longer in a state of severe asthma is to allow the disease to become progressively more severe as time goes on. To rely on injections of adrenalin to take care of recurrent

asthma is to invite subsequent serious disability in most patients with bronchial asthma. Our experience indicates that the more frequent adrenalin injections become, the more likely is the patient to develop a state of refractoriness to adrenalin and, therefore, of severe asthma. Adrenalin in any form provides a transient release of bronchial spasm, but it should not be considered as a measure which promotes progressive bronchial relaxation.

Repeated use of aminophylline does result in progressive bronchial relaxation in most patients with severe asthma. It is true that a certain number of patients will become refractory to aminophylline. Under these circumstances, inhalation of helium-oxygen mixtures, or rectal instillation of anesthetic doses of ether, or one of the procedures outlined in this paper, may be employed. Since intravenous injection of aminophylline twice a day for a week and once a day for a series of three weeks to three months is impractical, the rectal instillation of adequate dosages of aminophylline has been resorted to. Fortunately, this route of administration when used carefully will result in a relief of the symptoms of asthma comparable to that achieved by intravenous injection. Furthermore, the rectal employment of the drug is far less apt to create the dizziness and other manifestations of circulatory disturbance which intravenous treatment at times produces.

The complete program of bronchial relaxation includes, in addition to aminophylline, all other measures which result in bronchial relaxation. A new conditioned reflex may be set up in the patient in which his response to the environment in which he lives is different than it was previously, despite the existence of allergic factors over which the patient has no control. Physiologically directed therapy may, therefore, be appraised as a specific remedy for treatment of intractable asthma, although it is admitted at the outset that a final cure of the disease is neither aimed at nor expected. This principle of treatment however, makes it possible for many patients who otherwise endure more or less chronic and severe asthma to be free from the severe manifestations of the disease for the greater part of the time.

Variable degrees of constriction in the bronchial passageway occur in chronic pulmonary disease. This narrowing of the lumen of the bronchi may be caused by inflammatory swelling or by bronchial spasm. In either event the principles of treatment described for bronchial asthma are frequently applicable to conditions such as bronchiectasis, pulmonary fibrosis and emphysema, chronic bronchitis and bronchiolitis. Increasing the diameter of the smaller bronchi aids, not only in the relief of dyspnea and in preventing the consequences of increased negative pressures on the pulmonary epithelium but also in facilitating drainage of retained secretions. In some instances this physiological approach towards the treatment of chronic pulmonary disease is of considerably more value than attempts to rid the patient

of old foci of infection which may have originally acted as causative factors in the condition

The intelligent use of oxygen treatment in patients with chronic pulmonary disease, in whom dyspnea and cough are the predominant features, may be of very considerable value in retarding the course of the disease and in providing increased comfort

It should be emphasized that the allergic factor should be investigated in all patients with bronchial asthma and the measures developed in the noteworthy advances in allergy should be employed whenever they are applicable, the use of physiologically directed therapy in bronchial asthma is offered as an *additional* helpful procedure to combat persisting or recurrent bronchial spasm in intractable cases

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# OBSTRUCTIVE PULMONARY EMPHYSEMA

JULIUS L. WILSON, M.D., F.A.C.P.\*

AND

THOMAS FINDLEY, M.D., F.A.C.P.†

EMPHYSEMA is a disease characterized pathologically by distention and inelasticity of the lungs and clinically by reduced vital capacity and dyspnea. Viewed as an immediate threat to life it is not particularly important, but it is a serious and common cause of prolonged distress. It seems appropriate to include an account of it in a symposium on chronic diseases.

The brilliant studies of Laennec<sup>1</sup> published in 1819 form the cornerstone of our knowledge of pulmonary emphysema, and his theories regarding the etiology and pathogenesis are still accepted in essence. Rokitsky<sup>2</sup> was the first pathologist to describe the microscopic changes by modern technic, Brown-Séquard<sup>3</sup> pioneered in its experimental production, and Sir William Jenner's<sup>4</sup> studies were enormously fruitful. Indeed, it may be said that little of a fundamental nature has been added since.

## PATHOGENESIS

Laennec was the first to appreciate the importance of bronchial obstruction in the production of chronic pulmonary distention. Pointing to the common occurrence of bronchial catarrh, he postulated that air drawn into the lung during inspiration became partially trapped. In 1845 Mendelssohn<sup>5</sup> and in 1857 Jenner<sup>4</sup> independently emphasized the importance of forced expiration in the production of alveolar distention. It is conceivable that violent expiratory efforts such as occur during cough may distend peripheral and unsupported alveoli, but prolonged muscular expiration can only compress the greater bulk of lung tissue.

There is agreement then regarding the importance of respiratory obstruction. Disagreement lies in whether pulmonary distention occurs during inspiration or expiration, but the weight of evidence appears to support Laennec's contention that it occurs chiefly during the inspiratory phase. Inspiration is always an active process, whereas expiration

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From the Section on Internal Medicine, Ochsner Clinic, and the Department of Medicine, Tulane University School of Medicine, New Orleans.

\* Associate Professor of Medicine, Tulane University School of Medicine, Visiting Physician, Charity Hospital in New Orleans, Associate in Internal Medicine, Ochsner Clinic.

† Assistant Professor of Clinical Medicine, Tulane University School of Medicine, Director of Section on Internal Medicine, Ochsner Clinic, and Visiting Physician, Touro Infirmary.

is a passive act dependent largely upon the elastic recoil of the lung tissue. If the bronchial passages are continuously narrowed, as in chronic bronchitis, or intermittently constricted as in bronchial asthma, it seems reasonable to expect that air will be drawn more readily into the lungs than expelled.

Various investigators have attempted to produce pulmonary emphysema in laboratory animals. Acute pulmonary distention has been observed to follow stimulation of the vagus nerves or drug-induced constriction of bronchial musculature. Chronic and irreversible enlargement and rupture of alveoli have been produced by techniques which obstruct the flow of air through the trachea, and similar changes have followed the exposure of animals to low barometric pressure for prolonged periods of time. The common denominator for all of these experiments is, of course, increased respiratory effort. Paine<sup>6</sup> has reviewed the literature on emphysema in animals and added observations of his own.

Quantitative evidence supporting the thesis of Laennec has been found by those who have measured intrapleural pressure under various circumstances. Normally, intrapleural pressure is subatmospheric during both respiratory phases. It should become more negative whenever greater inspiratory activity is required to move air through narrowed bronchial tubes, and this diminished pressure must inevitably lead to pulmonary distention and to an increase in residual air. Brill, Prinzmetal and Brunn<sup>7</sup> demonstrated experimentally that drug-induced bronchospasm resulted in diminished intrapleural pressure, and later Prinzmetal<sup>8</sup> confirmed this finding in clinical asthma. Others<sup>9</sup> demonstrated increased residual air during asthmatic paroxysms. Very much earlier Brown-Séquard had observed alveolar distention to occur after electrical stimulation of the vagal nuclei in dogs, and Kountz and Alexander<sup>10</sup> made direct measurements of a similar nature.

The thorax must of course, adapt itself to the progressive enlargement of the lungs. Since soft tissue gives way more readily than bony structure, the diaphragm becomes depressed and ultimately fixed in the inspiratory position. This is one of the most reliable signs of obstructive emphysema, and is a matter of great physiological import because the excursion of the diaphragm accounts for approximately 40 per cent of normal vital capacity. As the diaphragm becomes more and more useless, the accessory muscles of respiration grow in importance. The abdominal muscles attempt to compensate for the loss of diaphragmatic function but their effect is usually negligible, and the burden of respiration falls on the intercostal and accessory muscles. In time, therefore, the thorax becomes relatively fixed in an inspiratory position and the typical barrel-shaped chest achieved. Whenever the diaphragm can descend no more and the chest wall expand no further intrapleural pressure then becomes positive and remains so throughout

the respiratory cycle. A positive intrapleural pressure imposes an added burden not only upon the respiratory act but upon the circulatory system as well, and sets up a train of events which will be referred to later.

The forces which make expiration possible are complex and need not be described here in detail. It is sufficient to state that pulmonary elasticity is an extremely important factor, since expiration is normally a passive process. Once the ability of the lung to resume its former volume is lost, emphysema becomes irreversible. Infection, prolonged distention and perhaps an inherent tissue weakness all contribute to the loss of elasticity of the lung, which is such a central feature of the disease. Christie<sup>11</sup> showed by simultaneous measurements of tidal air and intrapleural pressure that the normal lung is an almost perfect elastic body and that this ability to recoil is greatly diminished or altogether lost in advanced emphysema. Intrapleural pressures approaching atmospheric indicate that pulmonary distention is irreversible.

It should be stated that other theories concerning the pathogenesis of emphysema exist but none of them has received appreciable experimental or clinical support. Freund<sup>12</sup> believed that the thorax became fixed in its characteristic inspiratory position because of primary ossification of the costal cartilages, and he devised a surgical treatment which later proved unsuccessful. Loschke<sup>13</sup> showed how kyphosis of the thoracic spine may enlarge the thoracic cage in the anteroposterior diameter and maintained that pulmonary distention was secondary to this mechanical distortion. Kountz and Alexander<sup>10</sup> and Kerr and Lagen<sup>14</sup> have shown how a "postural" or nonobstructive type of emphysema may result from skeletal deformities and have performed a great clinical service in separating the two types. Suggestions that emphysema is the result of primary atrophy of elastic tissue, of nutritional changes in the alveolar walls, and of hereditary defects have not gained support.

#### PATHOLOGY

The essential pathologic change consists in enlargement and coalescence of terminal alveoli. The septa between adjacent alveoli become so perforated and the remnants so atrophied that large air sacs are formed, a process which considerably diminishes the surface area of the available respiratory endothelium. Evidence of interstitial inflammation is often seen microscopically. Early in the disease the capillary beds may be unaffected but progressive distention leads to obliteration of blood supply and to lymph stasis as well.

Grossly, the lungs are pale and irregularly pigmented. They fail to collapse when the thorax is opened and may be voluminous enough to fill the supraclavicular spaces, cover the precordium and anterior mediastinum and depress the diaphragm. They feel dry and bloodless, Laennec likened them to a pillow of down. There may be subpleural



bullae and blebs of various sizes, the rupture of which may result in spontaneous pneumothorax. Atheroma of the pulmonary artery is common

## Lung Volume and Its Subdivisions

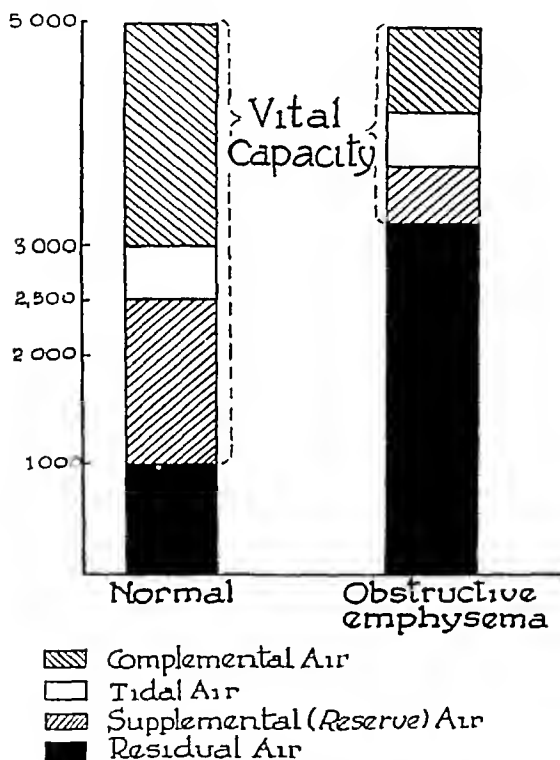


Fig. 38—Effect of obstructive pulmonary emphysema upon the components of the total lung volume

### RESPIRATORY CHANGES IN CHRONIC OBSTRUCTIVE EMPHYSEMA

As a consequence of the loss of pulmonary elasticity it is impossible for the patient to empty the lungs as fully as a normal person. The

residual air of the lungs is thus greatly increased, whereas normally it is around 1000 cc after the deepest possible expiration, in well developed emphysema the residual air may be as much as 3000 or 3500 cc. The tidal air is somewhat increased to compensate for the diminished respiratory surface of the lung. The complementary air is greatly decreased by the fact that the chest is already in full inspiratory position, and the supplemental air is only moderately decreased. The vital capacity is thus decreased anywhere from 20 to 60 per cent, principally by a diminished volume of complementary air (Fig 38).

Expiration, which is normally passive, becomes active. In addition to the internal intercostal muscles, all the accessory muscles of expiration are called into play. The diaphragm, no longer pulled up by the elastic

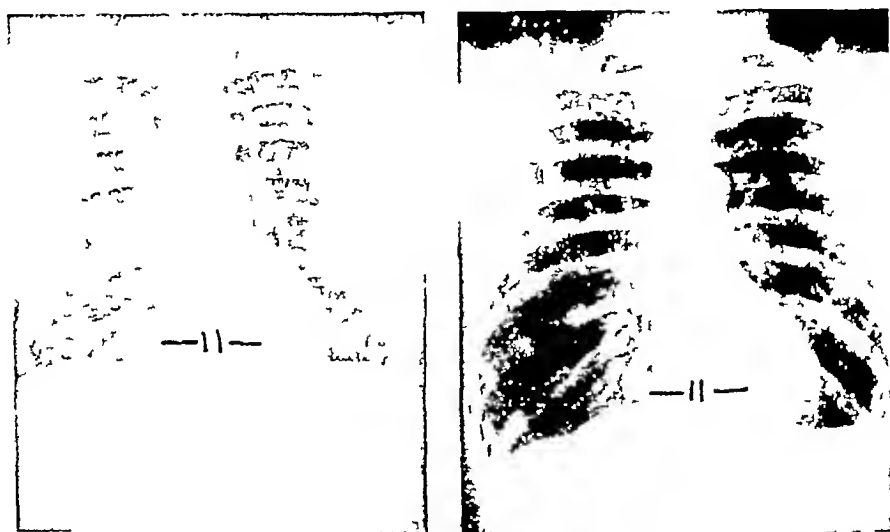


Fig 39—Depression and immobility of the diaphragm in emphysema. *Left*, full inspiration, *right*, full expiration. The horizontal lines mark the eleventh rib posteriorly.

recoil of the lungs, assumes a low position and hence loses much of its efficiency as a muscle of inspiration. Its contraction in this position may actually narrow the lower part of the chest and its motion may be paradoxical. The abdominal muscles are frequently relaxed in the patients with pulmonary emphysema, and consequently fail to support the abdominal viscera and to raise the diaphragm on expiration (Fig 39).

Incomplete mixing of gases in extremely emphysematous lungs produces an interesting distortion of acid-base balance. Since alveolar carbon dioxide tension is high, plasma bicarbonate rises and the plasma chloride falls. These changes superficially resemble those seen in certain types of alkalosis, but they are really due to excessive carbonic

acid. It is doubtful whether this mild acidosis contributes much to the clinical picture.

There is no entirely satisfactory explanation for this retention of carbonic acid and for the anoxemia which commonly accompanies advanced cases. The latter is, of course, responsible for the cyanosis and the polycythemia so frequently seen in this disease.

#### CIRCULATORY CHANGES IN PULMONARY EMPHYSEMA

The intrathoracic pressure is negative as a result of the elasticity of the lungs and the difference between the size of the thorax and the size of the lungs at rest. This negative pressure in the potential pleural space, acting on the mediastinum, contributes materially to the return of the blood to the heart by the great veins. Moreover, its fluctuation from  $-6$  cm. of water to  $-3$  cm. of water pumps the blood into the vessels and into the auricles of the heart. With the loss of elasticity which characterizes pulmonary emphysema, the intrathoracic negative pressure approaches atmospheric. It varies from  $-1$  to  $-2$  cm. of water on inspiration and  $0$  to  $+2$  cm. of water on expiration. Blood returning to the heart is, therefore, drawn into the thorax by a much less negative pressure on inspiration and may actually be held back by the positive pressure on expiration. The amplitude of the change in pressures between inspiration and expiration also being reduced, the pumping action is much feebler.

The effect upon the lesser circulation is similar. Both blood and lymph in the lungs themselves are not moved along by as great a change in intrathoracic pressures. In a normal person the pumping action of the changing intrathoracic pressures contributes little to the resting circulation of blood through the lungs. Under conditions of violent exertion with physiological dyspnea, the contribution of rapidly and widely changing intrathoracic pressures to pulmonary circulation is much greater. Both at rest and on exertion the flow of lymph from the lungs is chiefly dependent upon the changing intrathoracic pressures. The decreased amplitude of the respiratory fluctuations and pressures in emphysema would tend to allow lymph stasis in the lungs. However the shift toward atmospheric, or above atmospheric, level may actually squeeze the lymph out of the lungs on expiration. Clinically it is noteworthy that pulmonary edema is not a complication of pulmonary emphysema as long as the cardiac function is adequate.

#### PHYSICAL SIGNS

The diagnosis of pulmonary emphysema is one which may be made by careful inspection alone. The *form of the thorax* and the *mode of breathing* are the chief physical signs. With the overexpansion of the lungs the thorax tends to approach a roughly spherical shape—maxi-



Expiration 36 inches



Inspiration 37½ inches

Fig 40—Patient with obstructive pulmonary emphysema showing shape of thorax and its fixation in the inspiratory position. Note use of accessory muscles of respiration.



Fig 41—Far advanced pulmonary emphysema. Note the depressed diaphragm, the radiolucence of the lung fields, the bullae at the right apex and the dropped heart.

nal volume for a closed space with fixed surface area. This results in the "barrel-shaped" chest with increased dorsal kyphosis, anteriorly arched sternum, short neck, horizontal ribs and wide subcostal angle. In this position of deep inspiration the respiratory excursion of the ribs is diminished, and the thorax seems to move more or less as a whole. The accessory muscles of respiration are called into play, both on inspiration and on expiration, with the slightest exertion (Fig. 40). Expiration is considerably prolonged and active. Frequent additional findings on inspection are cyanosis of the lips and nail beds, and some degree of clubbing of the fingers.

The other physical signs are corroborative. On percussion there is a uniform hyperresonance over both lungs extending over the normal area of cardiac dullness and almost to the bottom of the costophrenic sulcus. The deep liver dullness is obliterated. The breath sounds are diminished in intensity, with the expiratory phase prolonged but not changed in pitch. The heart sounds are distant. Roentgenograms of the chest show an abnormally clear lung in contrast with the hilar markings (Fig. 41).

#### DIFFERENTIAL DIAGNOSIS

There are relatively few conditions which offer any difficulty in differentiation from obstructive emphysema. Overdistention of the lungs from *severe physical exertion*, *high altitude* or *bronchial asthma* may temporarily simulate emphysema. The circumstances under which the distention occurs are sufficient, as a rule, to indicate the cause. The periodicity and typical form of asthmatic attacks plus the history distinguish bronchial asthma from obstructive emphysema.

It must be emphasized that inspection of the thoracic cage alone may lead to errors in the diagnosis of chronic obstructive emphysema if not checked by functional study of the lung. In patients of the hypersthenic body type the thorax may appear to be barrel-shaped. When such persons are middle aged, or past middle age, and when they are obese, this appearance is often striking. These patients are often dyspneic when erect and have no shortness of breath when lying down. On further examination, it is found that in the absence of true emphysema the chest expansion is good, expiration is passive, the percussion note is not unduly hyperresonant, the breath sounds are normal, the diaphragm is high and the vital capacity is not materially reduced. This is the picture of *postural emphysema* described by Kerr and Lagen.<sup>14</sup>

Thoracic deformity due to increased *kyphosis of the dorsal spine* may also simulate pulmonary emphysema and possibly may in time produce some degree of emphysema as the lung loses its useful elasticity. As in postural emphysema associated with body build and obesity already described the function of the lung is not seriously impaired, at least at first. Chest expansion is good, percussion note is not hyperresonant, the breath sounds are normal, the diaphragm descends

freely and the vital capacity is only slightly reduced. Cyanosis and clubbing of the fingers are not observed in either of these conditions.

The differential diagnosis of *cardiac decompensation* may give more trouble, particularly in the person with a large and deep thorax. Dyspnea, orthopnea and cyanosis are found in both emphysema and cardiac failure. Dependent edema and enlargement and tenderness of the liver are not seen in emphysema unless there is also an added element of right sided heart failure. However, there may be some degree of left sided failure without these signs. The venous pressure may be increased in emphysema as in cardiac failure, but seldom to a pronounced degree. The vital capacity is reduced in both conditions. In the absence of definite evidence of cardiac enlargement or physical signs of cardiac disease, the electrocardiogram and the circulation time must be depended upon to furnish the critical evidence as to whether pulmonary emphysema or some degree of cardiac decompensation is responsible for the patient's symptoms.

It should be borne in mind that in actual practice the line between postural emphysema and obstructive emphysema on the one hand and between obstructive emphysema and cardiac failure on the other is not always sharply drawn. The patient with postural emphysema at the age of forty may have obstructive emphysema at fifty-five as a result of repeated infection and a loss of pulmonary elasticity. In patients with obstructive emphysema of long standing, cardiac decompensation eventually develops. Therefore, transition phases and combinations of emphysema and cardiac decompensation are seen as frequently as the simple types of these conditions.

#### PREVENTION AND TREATMENT

**Prevention**—The fundamental cause of emphysema, namely, the gradual loss of pulmonary elasticity, cannot be prevented. The contributory causes which produce bronchiolar obstruction should be combated in so far as possible. Bronchospasm due to asthma should be treated and the young asthmatic patient should be protected from recurrent attacks by desensitization or by removal from the environment in which asthma occurs. Recurrent and persistent bronchial infection should be treated by attacking the cause, if possible. Infected nasal accessory sinuses, infected tonsils and infected gums often are responsible for chronic bronchial infection and can be treated. Chronic irritation of the bronchial mucosa by dust, smoke and smoking may contribute to the prolongation of bronchitis. Such irritants should be avoided entirely or minimized by protective measures. When acute bronchitis occurs, it should be treated energetically and thoroughly until cured.

**Treatment**—The treatment of obstructive emphysema is largely the amelioration of an irreversible condition.

**DRUGS**—Drugs are often useful in relaxing bronchospasm and in thinning or decreasing the bronchial secretion *Ephedrine sulfate* is a valuable remedy which gives considerable relief to some patients. The action of epinephrine is too transitory to do any lasting good. In a recent case of obstructive emphysema without asthma the vital capacity rose from 1500 cc. to 2300 cc. within ten minutes after the subcutaneous administration of 1 mg. of epinephrine. Similar but less dramatic results may be obtained by the continuous administration of ephedrine. *Atropine* both dilates the bronchi and diminishes the bronchial secretion. It should be given in sufficient dosage to produce definite clinical effects.

The *expectorants* are helpful in cases in which the secretions are thick and tenacious. Inhalations of 5 to 10 per cent carbon dioxide and oxygen for a few minutes three to four times a day furnish probably the most effective method of loosening and clearing the secretion. Unfortunately, this treatment is seldom available outside of the hospital. Potassium iodide in full doses, syrup of iodic acid or ammonium chloride in sufficient dosage may be used. The following prescription may be found useful.

R

Ephedrine sulfate	10
Tincture of belladonna	30.0
Potassium iodide	36.0
Syrup of cherry	120.0
Water to make	240.0

Label Teaspoonful every 4 hours.

**MECHANICAL AIDS**—Since the malfunction in pulmonary emphysema is largely a difficulty in expiration due to the loss of pulmonary elasticity, a large number of methods have been suggested for overcoming this difficulty. *Exercises* have been suggested to improve the expiration. These generally consist of forcible expiration aided by pressure of the hands on the lower ribs. Unfortunately, the exercises are only of temporary benefit and the difficulty is continuous, few patients will persist in such exercises.

*Belts* to support the abdomen and hence to elevate the diaphragm have been devised by Kountz and Alexander<sup>10</sup> and Kerr and Lagen.<sup>11</sup> A great many of the sufferers from obstructive emphysema are relieved by these belts. It is difficult to determine in advance which patient will obtain relief from such support of the diaphragm. Such a belt must support the whole abdomen and actually raise the diaphragm so that in its more normal position it may function effectively on inspiration. The belt must be elastic to a certain extent to allow the abdominal wall to expand as the diaphragm descends. By trying manual support of the

abdomen or by applying an elastic bandage around the abdomen and observing the effect under the fluoroscope, one may obtain some idea as to whether a belt of this type will be beneficial

*Inhalations* of oxygen and helium mixtures will, of course, temporarily relieve the difficulty in respiration. However, it is obvious that such measures can be applied only in exceptional cases

**SURGICAL TREATMENT**—Operative treatment has been attempted in the past on the basis of various theories of the production of emphysema. It has not been successful. Mobilization of the costal cartilages or other measures to change the mobility of the thoracic cage cannot overcome the fundamental difficulty in the loss of elasticity in the lungs

**CLIMATIC TREATMENT**—Many of the patients with obstructive emphysema can lead useful lives and maintain a general level of health until a superimposed respiratory infection increases the obstruction and leads to true disability. This is most apt to occur during the colder months. Also, the patient subject to bronchial asthma may be unable to escape the antigen causing the bronchial spasm in his normal environment. The change of climate, preferably to one that is warm and dry, may thus be the most important therapeutic agent in prolonging the life and usefulness of these types of patients. The southern half of Florida, southern California, or certain parts of the southwest may offer a haven to such patients. Health resorts with an altitude much above sea level may, on the other hand, lead to serious anoxemia in patients who have a high degree of obstructive pulmonary emphysema

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# TREATMENT OF THE CHRONIC ANEMIAS

PAUL REZNIKOFF, M D \*

## GENERAL REMARKS

IN recent years such great advances have been made in the study of the causes and treatment of the anemias that this field has become a *scientific* part of clinical medicine. Nevertheless, the therapy encountered in daily practice frequently demonstrates little if any appreciation of the fundamental contributions to the subject. Many patients are given "shotgun" remedies so that no knowledge of a possible effective drug can be determined. This may eradicate all clues when it becomes necessary to diagnose the cause of the condition. Such procedures also are costly, time-consuming and inefficient. Indeed, it is not uncommon to encounter patients who have been treated for "anemia" because they have complained of fatigue or similar symptoms, in whom no blood study has been made to show the existence of any deficiency. In fact, few patients are investigated adequately to determine the cause of their anemia. There is no excuse for such a state of affairs, because in most cases the examinations are simple and can be performed in any physician's office. While it is obvious that some patients have obscure blood dyscrasias, the etiology of which defies even the most careful investigation, most anemias can be diagnosed and of these many can be treated successfully.

**Why Patients with Anemia Are Often Poorly Treated**—Some of the reasons patients with a decrease in red blood cells and hemoglobin are poorly treated are

1 It is not always realized that anemia is merely a sign of many diseases, and its treatment without an understanding of its cause is no more logical than treating fever without determining its etiology. *Anemia is never primary, always secondary*

2 Many physicians seize upon anemia as something tangible to treat rather than go through the time-consuming and laborious procedure of eliciting a complete history and performing an adequate physical examination which in the long run will probably save time and may result in the eradication of the cause of the condition. If the depression of erythrocytes and hemoglobin is only moderate, it is probable that the patient's symptoms and signs are not due to the anemia per se but are

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From the New York Hospital and the Department of Medicine, Cornell University Medical College, New York City

\* Associate Professor of Clinical Medicine, Cornell University Medical College, Attending Physician, New York Hospital, Visiting Physician, Bellevue Hospital

due to the same underlying disease which is producing the red blood cell and hemoglobin decrease as one of its effects

3 Some practitioners feel that "shotgun" remedies will do no harm and may cure the complaints and they will thus save themselves considerable trouble.

4 The simple basic laboratory examinations necessary to classify an anemia are not generally known, nor are the early evidences of response to therapy clearly appreciated.

**Basic Procedures in Diagnostic Survey**—Before discussing therapy it is desirable to enumerate the general procedure to follow in studying a patient and it is also necessary to have some simple classification of the main causes of anemia. The basic examinations are the following

- 1 A complete history paying special attention to familial diseases, bleeding dietary abnormalities, contact with toxic substances, drug administration, soreness of the tongue, paresthesias, gastro-intestinal symptoms, and jaundice.
- 2 An adequate physical examination including eyeground studies, and pelvic and rectal examinations
- 3 Urine examination.
- 4 Red blood cell count hemoglobin determination by an acceptable method, white blood cell and differential counts.

If possible it is desirable to have

- 1 An hematocrit determination.
- 2 Reticulocyte counts before treatment is instituted and at proper times after therapy is begun.
- 3 Stool examination for occult blood and for parasites and ova.
- 4 Gastric analysis with histamine stimulation and perhaps x ray studies of the gastro-intestinal tract.

In some cases it may be necessary to have a hypotonic saline test (fragility test) performed and a bone marrow study

### CLASSIFICATION

In order to treat erythrocyte and hemoglobin deficiency intelligently, it is essential to know the cause or the type of the defect. Anemias may be classified etiologically or according to cell size and hemoglobin content.

In itemizing the various causes of anemia, acute hemorrhage is usually not listed since the blood will return to normal in a previously healthy individual due to adequate stores of iron and other substances necessary for red blood cell and hemoglobin production

**Classification Based on Etiology**—A simple classification of reduction of red blood cells and hemoglobin based on etiology is the following

#### I Deficient Bone Marrow Function

##### A Faulty bone marrow nutrition

##### 1 Iron deficiency

(a) Chronic blood loss

(b) Defective iron ingestion or absorption

(c) Pregnancy

- 2 Extrinsic or intrinsic factor deficiency
- 3 Protein deficiency
- 4 Thyroid substance deficiency
- 5 Copper and other heavy metal deficiency
- B Depression of bone marrow
  - 1 Toxic (nephritis)
  - 2 Chemical (benzol, gold salts, sulfonamides, arsphenamine)
  - 3 Physical (x-ray and radium)
  - 4 Chronic infections
  - 5 Mechanical (leukemia, Hodgkin's disease, neoplasms)
  - 6 Refractory or aplastic anemia
- II Hemolytic Anemias
  - A Intrinsic
    - 1 Hemolytic, spherocytic jaundice
    - 2 Sickle cell anemia
    - 3 Paroxysmal, nocturnal hemoglobinuria
    - 4 Hemolysis due to isoagglutinins and isohemolysins
    - 5 March hemoglobinuria
  - B Extrinsic
    - 1 Malaria
    - 2 Hemolytic streptococcus or staphylococcus infections
    - 3 Sulfonamides
    - 4 Lead
    - 5 Favism
    - 6 Sensitization to Rh factor

**Morphologic Classification**—A morphologic classification based upon cell size or volume and relative hemoglobin content may be of considerable aid to the physician in diagnosing the type of anemia. In order to determine these factors it is necessary to have a red blood cell count, a hematocrit reading and a hemoglobin value. From these factors, volume index or mean corpuscular volume and color index can be calculated. On the basis of these findings, a classification can be made according to cell volume and relative hemoglobin content. While all combinations may be possible, as a rule the following morphologic types are found:

- 1 Normocytic, normochromic anemias (due to renal disease, many cases of aplastic anemia, and following infection)
- 2 Microcytic, hypochromic anemias
  - (a) Iron deficiency
  - (b) Mediterranean anemia
- 3 Macrocytic, hyperchromic anemias
  - (a) Pernicious anemia
  - (b) Sprue
  - (c) Carcinoma of the pylorus
  - (d) Cirrhosis
  - (e) Acute leukemia
  - (f) Aplastic anemia
  - (g) Bothriocephalus latus infestation
  - (h) Pregnancy
  - (i) Gastro-intestinal lesions such as fistulas

## THERAPY

With the above-mentioned facts in mind we are now prepared to consider the treatment of the various types of anemia, which will be discussed in the order of the etiologic classification presented previously.

**Iron Deficiency Anemias**—It is most important to remember that iron therapy is of value only for patients suffering from iron deficiency and in no other anemia. Since there are only three causes of iron deficiency—chronic blood loss, faulty iron intake and loss of iron to the fetus by a pregnant mother—the administration of iron in any other condition is not indicated. When one considers the almost universal habit of prescribing iron to all anemic patients regardless of the cause, the absurdity of such practice is obvious. Moreover, Balfour and his co-workers<sup>1</sup> have shown that the absorption of iron depends upon only one factor and that is the depletion of the body storehouses of iron. No matter how low the hemoglobin may be, iron therapy can be of no help unless there is a deficiency of iron in the supply depots of the organism.

It is important in the treatment of iron deficiency to determine the cause for such a defect. If the patient is bleeding, every effort must be made to stop such blood loss. This is relatively simple in cases of bleeding hemorrhoids or in patients who bleed from fibroid tumors. It is not as easy to treat a bleeding peptic ulcer and much more difficult to prevent bleeding from esophageal varices secondary to cirrhosis of the liver. But in all cases an attempt must be made to learn the cause of iron deficiency. In "idiopathic," hypochromic, microcytic anemia of women, especially after menopause, no apparent blood loss may be found but the anemia may have begun in early years during periods of menorrhagia or in previous pregnancies.

Faulty iron ingestion usually produces anemia in growing children or in girls who are losing blood during menstruation. In such cases the problem is one of iron balance as shown by Heath.<sup>2</sup> Where no blood loss is present or no excessive demand for iron is found as in growth or pregnancy, faulty iron ingestion does not cause iron deficiency. For example, malnourished elderly men who have no blood loss and even show evidences of pellagra or scurvy rarely have any appreciable anemia, and certainly no signs of lack of iron.

The classical picture of depletion of iron is hypochromia, microcytosis, low color index and low volume index or mean corpuscular volume. In some cases of long standing, anemia of this type a normocytic picture may be found but this is not usual. In addition to pallor, dyspnea on exertion, rapid pulse rate, slight fever, dependent edema and low blood pressure, it is not unusual to find brittle fingernails, sore mouth, especially at the angles, dysphagia, dry hair, and in some cases a palpable spleen.

If the diagnosis of iron deficiency is established and the cause of the condition is corrected, if possible, the treatment is specific and simple—namely, the administration of iron in adequate dosage, over a proper time interval and under clinical and hematological control. Many types of iron have been used and in most cases have been successful. However, the object of iron therapy is to give the patient a cheap, effective and nonirritating remedy. Most therapists have found that ferrous salts are more easily tolerated by patients than ferric salts or reduced iron. For the average adult patient, *ferrous sulfate* has been proved to be an efficacious remedy. This may be prescribed in capsule or tablet form. For example, an effective prescription is ferrous sulfate, exsiccated USP, 0.2 gm (3 grains) containing about 60 mg of iron. In order to eliminate irritation of the stomach, the medication should be given immediately after meals. To further minimize possible gastro-intestinal distress, it is a good policy to start with one capsule or tablet following each meal and increase the dose daily and gradually by one capsule or tablet a day (not per dose) until the patient is receiving three capsules or tablets after each meal. This would provide an intake of somewhat more than 0.5 gm of iron a day, which should be ample for most patients. If it is found that such a dosage causes gastro-intestinal disturbances, such as epigastric discomfort, nausea, diarrhea or constipation, the dose can be reduced and maintained at the predistressing levels.

More easily tolerated than the solid ferrous sulfate is the drug in liquid form and this is especially true in individuals who have difficulty in swallowing tablets or capsules and in children. A good prescription is *elixir of ferrous sulfate*, 4 cc, three times a day after meals. This elixir contains 0.1 gm ( $1\frac{1}{2}$  grains) of ferrous sulfate in each 4 cc or 38 mg of iron. In adults it is desirable to increase the dosage 4 cc a day until the patient is receiving 12 cc three times a day after meals, or almost 350 mg of iron a day. Since most patients must take iron medication for long periods—not less than a month and in some cases indefinitely—the total quantity ordered should be adequate, 300 capsules or tablets and 500 to 1000 cc of the elixir at a time.

A few patients may be intolerant to ferrous sulfate. It has been found that many of these individuals can take *ferrous gluconate* in fairly adequate amounts,<sup>3</sup> as 0.3 gm (5 grains). Each tablet contains 36 mg of iron. The dosage is started at one tablet after each meal and increased gradually until the patient is receiving nine tablets a day, unless gastro-intestinal symptoms occur. While such dosage affords only 325 mg of iron a day, it is probable that this is adequate in most cases. In some patients it has been found that good response is obtained with as little as three tablets or slightly more than 100 mg of iron a day.

Some clinicians still use many of the older iron remedies and if these cause no untoward effects, there is no objection to them. One of these

is 50 per cent *aqueous solution of ferric and ammonium citrate*, 4 cc., taken through a tube or straw with meals to avoid staining the teeth. This affords 6 gm ( $1\frac{1}{2}$  drams) of the iron compound a day or 1 gm (15 grains) of iron. Another of the older remedies is *ferrous carbonate* (Blaud's mass), 0.3 gm (5 grains), four capsules three times a day after meals, which gives 380 mg of iron a day. The capsules are preferable to the pills and the medication should be freshly made to prevent oxidation to the ferric state which would result in poor absorption.

Many patients suffering from iron deficiency anemia are found to be achlorhydric or hypochlorhydric. Some of these individuals fail to respond adequately to iron and in these cases it is desirable to give with meals *dilute hydrochloric acid*, U.S.P., 2 to 4 cc. diluted with half a glass of fruit juice or water to which sugar is added. The liquid is sipped through a tube or straw to protect the teeth. If a patient must have his meals outside of his home, capsules of acidulin may be given with meals, each capsule being equivalent to 0.6 cc (10 minims) of hydrochloric acid or glutamic acid hydrochloride—0.325 gm equivalent to the same quantity of acid.

In pregnancy some obstetricians believe it advantageous to prevent iron deficiency anemia by giving the mother iron therapy as a prophylactic, 300 mg of iron a day being considered adequate. All physicians do not consider such therapy necessary or even desirable and believe that when the pregnant woman has had an adequate diet she will not develop iron deficiency. Moreover, it must be remembered that a moderate reduction in red blood cell count and hemoglobin in the latter months of pregnancy is due to blood dilution rather than to anemia and is considered physiological by many workers.

The effect of iron therapy depends in the last analysis upon the response of the patient. If a reticulocyte peak is obtained within five to ten days after therapy is started, it is certain that the hemoglobin level will reach normal with continued treatment. The height of the reticulocyte peak will be inversely proportional to the initial hemoglobin level. A normal blood count should be attained in three to four weeks after the onset of treatment. Thereafter maintenance therapy should be continued and red blood cell counts and hemoglobin determinations may be made once a month. Some patients will require no further treatment after the blood has attained a normal level especially if the cause of the iron deficiency has been eradicated. But in many individuals, especially those with idiopathic hypochromic anemia and in cases of achlorhydria, iron therapy must be continued always to prevent a return of the anemia.

One important fact should be emphasized in a consideration of iron therapy. *Iron should be given by mouth and not by parenteral injection.* Not only are iron compounds toxic when injected but the amounts which can be given parenterally are of very little value. Many

physicians have been misled by reports which have reference to experimental work mainly in animals. If a patient cannot tolerate iron by mouth, it is quite certain that the injection of iron would be highly undesirable and valueless.

*Foods* which contain a high percentage of iron should be used especially when the anemia is due to faulty ingestion of iron. These are liver, kidney, meat, tripe, eggs, apricots, peaches, prunes, raisins, spinach, beet greens and whole grain cereals.

Most textbooks urge physicians to use certain *general measures* such as adequate physical and mental rest, fresh air, sunshine, massage and hydrotherapy. These are all desirable in any patient but cannot take the place of specific therapy. In the absence of these commendable hygienic measures, patients will recover from iron deficiency anemia with adequate iron therapy and the elimination of the cause of the defect.

While there is experimental evidence that such factors as Whipple's liver factor, chlorophyll and bile salts may aid in hemoglobin formation, there is no indication that any patient failed to respond to iron therapy because of the lack of these agents.

**Pernicious and Other Macrocytic Anemias**—*Liver extract* is a specific remedy for deficiency of intrinsic factor which is the cause of pernicious anemia. It is also effective in other macrocytic anemias such as the anemia of sprue, "tropical" nutritional macrocytic anemia, the anemia of *Diphyllobothrium latum* infestation, macrocytic anemia of pregnancy and the macrocytic anemias associated with hypothyroidism and some intestinal lesions such as gastrocolic fistula. It may also be of value in idiopathic steatorrhea or celiac disease. Macrocytic anemia found in carcinoma of the pyloric portion of the stomach may show some response when liver extract is given but obviously does nothing to cure the disease and sometimes such improvement prevents the diagnosis if x-ray studies of the stomach are not made. In cirrhosis of the liver, macrocytic anemia is not infrequently seen and liver extract sometimes produces an increase in red blood cell count. This, however, is not usually striking. Many of the above mentioned conditions may be due to deficiency in extrinsic factor, but even in such states liver extract has been found to be effective. Patients, suffering from malnutrition, especially of those foods which contain the extrinsic factor, may respond not only to liver extract but to a diet rich in meat or to large amounts of brewers' yeast.

Unless a patient has macrocytic anemia or one entirely or in part due to lack of intrinsic or extrinsic factor, there is no justification for the use of liver extract. Moreover, if there is no reticulocyte response in five to ten days and a conspicuous red blood cell rise within two or three weeks after onset of therapy, the continuance of liver therapy is not indicated. In many of the macrocytic conditions, liver therapy is only one factor in the treatment of the disease. For example in idio-



pathic steatorrhea, careful attention to diet, consisting of low fat, high protein, low starch, high simple carbohydrate and high vitamin intake is essential. Frequently, pancreatic therapy and measures to control diarrhea are necessary. It is impossible to review the complete therapy of all diseases in which macrocytic anemia occurs, but it must again be emphasized that the entire patient should be treated and not only his blood.

In order to simplify the problem of the use of liver extract, it might be well to describe its administration in an uncomplicated case of relapse in pernicious anemia. Since liver extract is not destroyed or excreted it is desirable to give more rather than less of the material. While the average patient may need only 1 U.S.P. unit a day, there is no method of standardizing the material except by the patient's response. Patients differ markedly in the amount of liver extract required.<sup>4</sup> One other fact needs emphasis and that is that intramuscular injection is the route of choice for administration. Only in the rare patient who is sensitive to parenteral treatment should oral therapy be considered. There is no good evidence that any one type of liver extract is superior to any other if the product has been accepted by the United States Pharmacopoeia. This statement holds true for both refined and crude extract.

The average patient should receive 15 to 30 units of an acceptable liver extract intramuscularly daily until the reticulocyte peak is reached that is, for one week to ten days. After this period the frequency of injection may be decreased to three times a week until the red blood cell count reaches 4,000,000. Then the periods of therapy and the amount will depend upon the patient's response. For example some individuals maintain a normal count on 15 units a month. A few may need 15 units a week. Other factors influence the patient's maintenance dose such as infections, neurological signs and symptoms and possibly arteriosclerosis. Certainly a patient who has paresthesias, a diminished vibratory sense and other neurological involvement should receive more therapy than a subject free from these. These patients should also take large amounts of vitamin B for their peripheral neuritis.

The following table gives some indication of the *expected reticulocyte response* at its peak if therapy is effective. The peak varies inversely with the initial red blood cell count before therapy is begun.

Initial Red Blood Cell Count	Average Percentage Increase of Reticulocytes	Minimum Percentage Increase of Reticulocytes
500,000	60	50
1,000,000	35	30
1,500,000	25	18
2,000,000	15	12
2,500,000	10	7
3,000,000	4	4

The question whether *hydrochloric acid* should be given in pernicious anemia cannot be answered in the same way in all cases. Most patients do not need hydrochloric acid, but in general individuals who complain of gastric distress or diarrhea and have no other reason to explain these symptoms do well when they take acid. This should be administered as outlined previously in the paragraph dealing with iron deficiency.

It is rarely necessary to give *iron* in pernicious anemia. Some authors feel that if the hemoglobin rise does not keep pace with the improvement in red blood cell count, iron therapy is indicated. However, if the patient does not have a real iron deficiency, it is not necessary to add another medication. In other words, true anemia rather than a relatively low hemoglobin value should determine the need for iron therapy. The patient rather than the blood count should be treated.

**Anemias Due to Other Nutritional Factors.**—One of the essential substances necessary for the proper production of hemoglobin and red blood cells is protein. Whipple<sup>5</sup> has demonstrated its importance. Anemia due to *protein* deficiency has been seen clinically in cases of marked malnutrition when the protein intake is especially low. Usually patients also suffer from multiple deficiencies when they are especially deficient in protein ingestion. If an individual has an adequate and well rounded diet, the protein is usually sufficient. However, in nephrotic conditions, where the urinary loss of protein is marked, it must be increased above the usual normal requirements.

While *copper* and other heavy metals are essential for the proper formation of hemoglobin, these elements are necessary in such minute amounts that they are amply provided by the ordinary diet or in the impurities found in medication. Therefore, there is no justification, except perhaps in infants, to add these substances. There is no evidence in ordinary practice that copper has any appreciable value when added to iron.

Much work has been published to suggest that *vitamins C and B* are advantageous in the treatment of nutritional anemias. Recently it has been shown that the anemia of scurvy is due to iron deficiency because of the concomitant low iron intake in vitamin C deficient diets and can be corrected by iron alone. As far as vitamin B is concerned, animal experiments are suggestive that some of the B factors are efficacious, but no conclusive experiments have been performed to indicate that vitamin B therapy is needed to correct human nutritional anemia.<sup>6</sup> Therefore, at the present time it is not considered necessary to add any vitamin to iron or liver therapy. The many pharmaceutical products which contain vitamins should not be used unless there is also evidence of vitamin deficiency.

**Anemia of Hypothyroidism**—Hypothyroid patients may show anemia which may be normocytic, macrocytic or microcytic. In such indi-

viduals, it is necessary to give, in addition to thyroid extract, medication for the blood deficiency. If the subject has a macrocytic condition, parenteral liver extract should be given as in pernicious anemia. In the microcytic type, iron should be administered as in the treatment of iron deficiency. Normocytic anemia in hypothyroidism also occurs and yields to thyroid therapy rather slowly. In such cases, some workers assume that the patient is suffering from iron and intrinsic factor deficiency and give both liver and iron in addition to thyroid extract. It is not known whether the anemia responds more rapidly to such therapy than to thyroid substance alone.

**Anemia of Pregnancy**—While this subject has been discussed previously, it is important to consider this state as an entity. In the first place, it must be reiterated that there is dilution of blood in the latter stage of pregnancy and that this is not a true anemia and cannot be corrected by iron or liver therapy. Iron deficiency has already been discussed. Also the true macrocytic anemia of pregnancy has been mentioned and its treatment with liver extract described. There are a few patients who have multiple deficiencies and these may have hypochromia and macrocytosis. However, the anemia may be pronounced and be of a normocytic, normochromic type. In such rare cases, it may be justifiable to give iron and liver. The frequent practice of administering iron and liver to all pregnant patients with even mild anemia is not a good procedure.

**Multiple Deficiency Anemia**—In severe malnutrition and in some iron deficient pernicious anemia patients, it has been found necessary to give an optimum diet and adjuvant iron and liver therapy. It is important to try to determine the predominant deficiency first and administer the indicated remedy. If a reticulocyte response can be followed for each hematinic, treatment can be undertaken more intelligently and, in the long run, economically, both with respect to finances and time.

**Duration of Therapy**—Pernicious anemia patients will have to be treated for the duration of their lives. They should be so instructed. The same may be true of many iron deficient individuals especially those suffering from "idiopathic" hypochromic anemia. Pernicious anemia of pregnancy usually disappears with the termination of pregnancy. Hypothyroid subjects whose anemia is corrected may need no further treatment for their blood if the thyroid status is maintained at a normal level.

**Depression of the Bone Marrow**—In most cases in which bone marrow depression occurs, therapy can be successful only if the depressing agent is removed or the causative factor is corrected. This is obviously not possible in *chronic nephritis*. In general the anemia runs parallel to nitrogen retention. Loss of blood due to long-continued and persistent hematuria even of microscopic amounts or frank bleeding from other parts of the body which occurs in uremia may contribute to the

anemia The only palliative treatment is transfusions, which should be given for symptoms and signs of anoxia.

The same therapy should be used in cases of *aplastic* or *refractory anemia* There is no evidence that iron, liver or any other therapy except transfusions is of help in this condition The purpose of transfusions should be to keep the patient comfortable and free from such disabilities as dyspnea and extreme weakness and not to correct the blood picture Transfusions probably do not stimulate the depressed bone marrow In determining the frequency of transfusions, the patient's economic status, activity, family obligations, and the realization that we are dealing with an incurable disease should all be considered by the physician Some individuals carry on quite well for years with transfusions of 500 cc on a few successive days every month, or few months Other patients need transfusions at much more frequent intervals Each case must be studied individually to determine a plan of treatment

Certain *chemical depressants*, such as sulfonamides and arsphenamine, may have only a temporary effect This may also be true of benzol and gold salts In other patients any of these chemicals may produce an irreversible condition and result in a true aplastic state of the bone marrow, and transfusions will be necessary to maintain life If the reticulocyte count is above normal it usually means that the bone marrow is functioning well and will recover eventually The same principle may be true for physical agents such as x-ray and radium

When the bone marrow is depressed because of chronic infections, therapy must be designed to cure the infection and improve the anemia by palliative transfusions

*Leukemia, Hodgkin's disease and metastatic lesions in the bone marrow* produce anemia by crowding out the erythrogenic tissue If irradiation therapy is successful, the blood will often show improvement It must be remembered, however, that irradiation itself may cause some bone marrow depression and should be administered with constant check of the blood count Often transfusions are necessary as a supportive measure until irradiation becomes effective

**Hemolytic Anemias —OF INTRINSIC ORIGIN —**The treatment depends upon the cause of hemolysis The most satisfactory hemolytic condition to treat as far as cure is concerned is *hemolytic spherocytic jaundice* of the familial type Splenectomy is specific therapy Although there is no change in the abnormality of the red blood cells, removal of the spleen will end hemolysis in almost all cases There is one feature of this condition which merits mention In preparing the patient for operation, transfusions may be necessary to raise the blood count However, these patients tend to hemolyze readily the donor's blood as well as their own and suffer transfusion reactions without obtaining optimum benefit from the transfusions Consequently, it is best to save

the transfusions for the operative and postoperative period if the blood count permits this procedure. Most individuals will stand an operation well if the red blood cell count is about 3,500,000 with a comparable hemoglobin value.

Certain of the hemolytic states do not yield to any therapeutic measure. *Sickle cell anemia* can be treated only symptomatically. There is no good evidence that splenectomy is of value. Transfusions may be necessary but these often given severe reactions. *Paroxysmal nocturnal hemoglobinuria* and *hemolysis due to isoagglutinins* and *isohemolysis* do not yield to therapy.

*March hemoglobinuria* is due to excessive physical activity or long-continued strain due to posture. Often this condition corrects itself and is not as a rule of a serious nature.

OF EXTRINSIC ORIGIN.—Hemolytic anemia due to extrinsic agents can be corrected, if not of an overwhelming nature, by treating the offending factor. This is true of *malaria* and *hemolytic bacterial infections*. Anemia due to *lead poisoning*, especially of the acute type, usually responds to the proper treatment of plumbism and with improvement, the blood returns to normal in time.

When the *sulfonamides* cause hemolysis, the decrease in blood count usually occurs soon after the drug is given. If the defect is moderate and the reticulocyte count is above normal, the patient usually recovers without any special treatment. If the anemia is severe, the drug may have to be stopped and transfusions given.

*Favism* is due to an anaphylactic reaction to the inhalation of pollen or eating the raw fava bean after previous sensitization. This type of hemolysis may prove fatal. It is prevalent in Italy, but only a few cases have been reported in this country. Prevention is, of course, the best type of therapy. During an acute attack, transfusions must be given.

Recently much light has been thrown on the cause of hemolytic anemia following transfusions to postpartum patients. It has been found that usually the donor frequently the husband has an Rh factor in the blood which is not present in the wife. She becomes sensitized to the Rh factor by the fetus who has inherited the positive Rh factor from the father. The recipient has thus developed an Rh antibody which in contact with the Rh antigen produces a marked reaction resulting in hemolysis. To avoid such a condition which may be fatal it is important to test the mother's blood for the presence or absence of an Rh factor. If the blood is Rh negative she must only be given blood from an Rh negative donor. It is also possible that repeated transfusions given from Rh positive donors to a negative recipient may eventually produce anti Rh antibodies in the latter and lead to severe hemolysis.

Many other hemolytic anemias have been described such as Lederer's acute hemolytic anemia and paroxysmal (cold) hemoglobinuria presumably due to syphilis. For these rare conditions the reader is referred to textbooks of hematology.<sup>†</sup>

**Transfusions**—It is beyond the scope of this paper to give a detailed account of the indications for transfusion or the methods of matching or administering blood. Since this is an important procedure in the treatment of many anemias, it should be pointed out that in most cases transfusions are only *palliative*. The purpose of transfusions is to tide a patient over until the cause of an anemia can be eradicated and the disease becomes self-limited. Transfusions are invaluable in correcting anoxia or preparing an individual for operation or irradiation, but the transfused blood does not become a permanent addition to the patient's circulation. It is therefore important to appreciate the transitory nature of the donor's blood and to emphasize the fact that anemias can be cured only when a person's bone marrow can manufacture red blood cells and hemoglobin normally.

### CONCLUSIONS

Anemia is only a sign of disease and its treatment depends upon an understanding of its cause and correlation of this depression of red blood cells and hemoglobin with the entire clinical picture. To treat anemia with "shotgun" therapy is usually uneconomical and often results in failure. Iron should be given only in iron deficiency states; liver therapy, in macrocytic anemias, and transfusions, to treat anoxia and as a palliative measure. Before therapy is started an adequate study should be made to determine the cause and type of the anemia so that logical treatment may be undertaken. Lack of therapeutic success may be due to the hopelessness of the patient's illness, but sometimes it is due to the failure of the physician to understand the nature of the condition and to appreciate the fact that all anemias are *secondary* to some pathological state in the patient. The patient rather than a blood picture must be treated.

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## CARE OF THE PATIENT WITH CHRONIC HEART DISEASE

EUGENE A. STEAD, JR., M.D.\* AND JAMES V. WARREN, M.D.†

THE treatment of congestive heart failure has gradually improved as the basic physiology of heart failure has become better understood. In order to understand the principles underlying therapy, let us trace the natural history of a patient with congestive heart failure.

As long as the heart is able to put out the blood required for the daily routine of the patient, heart failure does not occur. When the heart is not able to pump the amount of blood necessary to maintain the circulation at a normal level during the patient's daily routine, symptoms of heart failure develop. If, at this time, the patient is put at rest, the symptoms of heart failure will quickly disappear without medication. The heart is still capable of maintaining a normal circulation at rest. Only during activity is the heart inadequate. Studies of the cardiac output in the patient at this time will show that the resting cardiac output is within normal limits. Thus, the patient can be compensated for a time by reducing his activity and reducing the amount of blood pumped per twenty-four-hour period.

In time, regardless of limitation of activity, the cardiac output becomes inadequate and the symptoms of heart failure again develop. By the proper use of digitalis, the physician can strengthen the heart and cause it to pump blood more effectively. Again the symptoms of congestive failure disappear. After a time the cardiac output again decreases and in spite of digitalis and limitation of activity the symptoms of congestive failure reappear. The resting cardiac output will now be low and salt and water retention will occur even at rest. Because many of the symptoms of congestive failure result from the interference in function of the lungs and other organs due to excessive retention of salt and water, the patient can be kept comfortable even with a moderate decrease in cardiac output if such retention of salt and water is kept at a minimum. This can be done by the use of diuretics and by limiting the dietary intake of sodium. In time salt and water retention occurs in spite of constant therapy, and the patient becomes waterlogged and dies.

In summary, then, we can help the patient with congestive failure in three ways: (1) by rest so that the body requirements for blood are

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From the Medical Service of the Grady Hospital and the Department of Medicine, Emory University School of Medicine, Atlanta, Georgia.

\* Professor of Medicine and Chairman of the Department, Emory University School of Medicine. Visiting Physician, Grady Hospital.

† Instructor in Medicine, Emory University School of Medicine. Visiting Physician, Grady Hospital.

less and the daily output of the heart can be decreased without interfering with body economy, (2) by strengthening the failing heart with digitalis so that it can maintain an output compatible with the necessary activity of the patient, and (3) by eliminating the salt and water which tend to be retained when the cardiac output becomes insufficient to support the patient's daily routine of living. In the above discussion, for the sake of clarity, we used each of three measures separately. In practice we combine them.

### REST

The load on the heart can be eased in two ways: (1) by limiting the patient's physical activity and (2) by correcting any abnormal condition which causes the resting cardiac output to be elevated. Physical activity can be decreased by weight reduction if the patient is obese. He is instructed to be slow and deliberate in his movements, to walk slowly rather than briskly, to avoid stairs and inclines. He is given appropriate rest periods in the day and goes to bed at an early hour. If the patient is orthopneic, a cardiac bed is desirable. Sedatives should be used as necessary to insure restful nights. If the patient becomes more decompensated because of an acute infection, morphine by mouth at bedtime may be necessary to insure sleep. Certain diseases cause the resting cardiac output to be elevated, and a greater than normal amount of blood must be pumped to maintain the health of the patient. Congestive failure may be present in these patients at rest, even though the cardiac output is greater than it would be in normal subjects under similar conditions. Thyrotoxicosis, anemia, nutritional deficiency, arteriovenous aneurysm and patent ductus arteriosus all put strain on the heart even at rest. If such a condition is present, its correction may enable the heart to compensate and greatly improve the patient's prognosis.

### DIGITALIS THERAPY

That the administration of digitalis increases the ability of the failing heart to perform its work is generally accepted. This action of digitalis on the myocardium can be counted on both in patients with regular rhythm and in those with auricular fibrillation. Indeed, digitalis is beneficial in patients with myocardial failure even in the presence of complete heart block. The increased number of digitalis products now available presents a confusing array to the physician. There is little evidence, however, that any one preparation has a more beneficial effect on the myocardium or fewer toxic effects than any other. Therefore the choice of drug depends upon such factors as the rapidity of digitalization desired, the preferred method of administration, expense, and the doctor's experience with a given drug.

If rapid digitalization is not necessary, the old reliable powdered digitalis is still most widely used. Since this is a natural product, and



therefore variable, some method of biological assay is required. That amount of digitalis found to be equal in activity to one unit of the standard is labeled 0.1 gm. digitalis. In each of the last three editions of the United States Pharmacopoeia the standardization of digitalis has been modified. This has caused considerable confusion. In some localities U.S.P. X digitalis is still available. The reference standard for this digitalis was relatively weak and the method of comparison was the frog assay. Because the digitalis unit U.S.P. X happened to be approximately equal to the Hatcher-Brody cat unit, an independent unit not related to U.S.P. standards, physicians became accustomed to using the terms interchangeably. With the advent of U.S.P. XI, the reference standard was so increased in potency that one U.S.P. XI unit of digitalis was almost 50 per cent stronger than a U.S.P. X unit and hence no longer equal to the Hatcher-Brody cat unit. Finally, the latest edition, U.S.P. XII, standardizes digitalis against a new standard and by a different method (a cat method, but not that of Hatcher and Brody). The newest product appears to be midway in potency between that of U.S.P. X and XI. Thus, there are available at the present time three digitalis products varying so considerably in strength per unit that the difference in potency is clinically detectable. The physician should be aware of this difference in potency and know which product his patients are receiving. As the newer pure digitalis products become more available, much of the difficulty may be circumvented.

The individual requirement of digitalis for complete digitalization is quite variable, making a definite statement of dosage almost impossible. It has become apparent that much of this variation is due to differing efficacy of absorption of the drug from the gastro intestinal tract. In general about 1.5 gm. (U.S.P. XII) are required. The speed of administration depends upon the condition of the patient. As the point where digitalization can be expected is approached the doses should not be large, and before each is administered the patient should be questioned about early symptoms of toxicity. Particularly important is the loss of appetite which is often the earliest such symptom.

A physician should be familiar with at least one of the drugs available for rapid *parenteral* digitalization. In this clinic lanatocid C, a pure glycoside from digitalis lanata, has been used and proved very satisfactory.<sup>1</sup> The usually accepted digitalizing dose of 1.6 mg., given either intravenously or intramuscularly, and most often in two equal doses, produces good clinical response with a low incidence of toxic effect. It is possible that the apparent lack of toxicity is due to the fact that this dose is slightly less than a complete digitalizing dose. Soon after the lanatocid C has been given digitalis leaf is started by mouth in doses of 0.1 gm. three times a day and continued at that dose until the patient has a satisfactory clinical response or shows evidence of toxicity.

## PREVENTION AND TREATMENT OF EDEMA

Measures for preventing the accumulation of salt and water are of primary importance in treating congestive failure. Whenever the degree of activity of the patient is increased beyond the capacity of the heart to pump blood, salt and water accumulate. In the early stages of congestive failure, this occurs during activity. Thus the patient develops edema while carrying on his usual activities. If, by rest, the degree of activity of the patient is decreased to where the heart is capable of maintaining a normal circulation, the edema subsides as the kidneys excrete the accumulated salt and water. In time, as the circulation becomes inadequate at rest, edema forms while the patient is in bed unless special measures are taken to prevent it.

The retention of the sodium ion appears to be the primary cause of edema in cardiac failure.<sup>2</sup> The exact mechanism by which this occurs has not been determined. The retention of chloride and water is apparently secondary to the retention of the sodium ion. Edema in congestive failure can be minimized in two ways: (1) by limiting the intake of sodium and (2) by increasing the excretion of sodium. The observation that retention of sodium is necessary for the formation of edema is of great importance, since it eliminates the need for decreasing the water intake in patients with congestive failure, provided their sodium intake is very low. Water does not accumulate in the patient with congestive failure unless that water can be made isotonic with body fluids by the addition of sodium chloride.<sup>3</sup> If the necessary sodium is not present, the water is rapidly excreted in the urine. It must be remembered that the sodium is present in the ash of most foods and that sodium retention with edema formation is possible even though the salt intake is limited unless acid-ash foods are selected. Schemm<sup>4</sup> has published diets which yield an acid-ash and contain not more than 0.5 gm of salt. If this diet is followed strictly fluids may be given freely. Many patients will not eat a low salt, acid-ash diet. If the patient is undernourished, it may be better to increase the salt intake so that the patient will take more food, and then to increase salt elimination through the kidneys by the use of diuretics.

**Diuresis.**—Patients who are no longer able to maintain an adequate cardiac output by rest or by the use of digitalis must receive diuretics at regular intervals. It is now recognized that dyspnea caused by heart failure is an indication for diuresis, though there is no demonstrable peripheral edema and though the venous pressure is normal. In many patients with left ventricular failure, edema accumulates in the lungs before it is demonstrable elsewhere. Attacks of paroxysmal nocturnal dyspnea may be prevented by regular use of diuretics. The diuretic selected and the frequency of its administration depend on the rapidity with which fluid accumulates. If the patient has chronic congestive failure and the heart has not compensated on rest and digitalis, the

physician must plan a long-range program of active treatment for the rest of the patient's life. The patient can usually be prevented from developing massive edema until his terminal illness. The most common mistake is to give the diuretic at too infrequent intervals.

The *xanthine diuretics* are useful because they can be given by mouth, but have the disadvantage of being much less powerful than the mercurial diuretics. There are many preparations available, the dosage varying somewhat with the particular product.

Mercupurin and salyrgan with theophylline are the *mercurial diuretics* in common use. The original dose should not exceed 0.5 to 1 cc. After the initial injection they are usually given intravenously in doses of 1 to 2 cc. at intervals of two days to two weeks, depending on the tendency of the patient to retain salt and water. These substances cause marked irritation when given subcutaneously and care must be taken to be certain that the needle is cleanly in the vein before the injection is carried out. If no veins are found it may be injected into the muscles of the buttocks. The mercurial diuretic is usually administered in the morning so that the resulting polyuria will not interfere with the patient's sleep. Many patients complain of weakness after marked diuresis. In rare instances toxic reactions may occur. If an injection of 1 to 2 cc. produces marked weakness, it is better to give smaller doses at more frequent intervals.

If the mercurial diuretic is ineffective, it may be supplemented by the administration of *ammonium chloride*. This is given in enteric-coated capsules in doses of 6 to 8 gm. daily for two to three days. At the end of that time the mercurial diuretic is given and the ammonium chloride discontinued. This routine is repeated as often as necessary to keep the patient free of dyspnea and edema.

*Urea* in doses of 90 gm. per day is an effective diuretic. It has the disadvantage of an unpleasant taste, but if the patient tolerates it, urea has the great advantage of being taken by mouth. It can be used alone or in combination with ammonium chloride and a mercurial diuretic. In the advanced stage of congested failure when the patient is a complete invalid, it may be necessary to give urea daily, mercupurin or salyrgan with theophylline in 2-cc. doses every second or third day and ammonium chloride in doses of 6 to 9 gm. for two to three days at five day intervals. These measures are combined with the low sodium acid ash diet.

**Other Measures to Control Edema**—In certain patients fluid tends to accumulate in the chest in spite of good cardiac care. The removal of this fluid by *thoracentesis* will allow the patient to breathe much more comfortably. At times one is surprised by the great improvement in dyspnea which results from the removal of a relatively small amount of fluid. Five hundred cubic centimeters of fluid in the chest of a person with normal lungs will not cause dyspnea. Five hundred cubic

centimeters of fluid in the pleural cavity of a patient whose vital capacity is greatly diminished because of edematous lungs from heart failure may cause marked dyspnea.

Certain patients with chronic mild failure complain of the fact that they have to void after a few hours in bed and that once they are awakened they cannot go back to sleep. These patients accumulate edema in the lower part of the body during the day because of the high hydrostatic venous pressure in the portion of the body below the heart. On going to bed, this fluid enters the circulation and is excreted by the kidneys so that after a few hours the patient has to void. If the patient lies down for a couple of hours after dinner, before going to bed, a portion of the excess fluid will be voided and the patient may not be awakened to void.

As the patient becomes more inactive, the edema in the lower extremities may be aggravated by the immobility. The lower extremities remain motionless for long periods of time. The venous pressure in them is high because of the hydrostatic pressure of the column of blood in the veins, and because of the lack of motion the lymphatic flow is very slow. This edema can be reduced by the use of *elastic bandages* applied before the patient rises and removed after he returns to bed. Some patients with advanced congestive failure are more comfortable in a chair than in a bed. A patient should not be forced to lie in bed if he prefers to sit up. Indeed, there may be danger in placing him in bed. The edema which has accumulated in the lower extremities remains there while he is in the chair. If placed in bed, the venous pressure in the lower extremities will be lowered and the fluid may enter the blood stream and be deposited in the lungs.

Any infection in the body may precipitate acute cardiac decompensation. Respiratory infections in particular are dangerous. The patient should have complete bed rest if he develops a cold, sore throat, or bronchitis. In patients with chronic heart disease, exacerbations of congestive failure are usually secondary to infection rather than to unusual exertion. If cough is troublesome it must be controlled by the administration of codein.

**Acute Pulmonary Edema**—As a result of infection, overwork, ingestion of large amounts of sodium chloride, omission of digitalis, too long intervals between the administration of diuretics, or because of progressive myocardial disease, sudden dramatic episodes of pulmonary edema frequently occur during the course of chronic heart disease. This can happen during the day, but it is particularly prone to occur during sleep. The patient awakens with marked dyspnea and orthopnea. He is frightened and apprehensive. The extremities are cold and the patient sweats profusely. The heart rate is fast, the arterial pressure is frequently elevated. The lungs are usually filled with moist râles and the patient may raise bloody, frothy sputum. In other patients bron-

chial spasm occurs, and the patient presents the clinical picture of asthma. In some patients the lungs are clear on auscultation because the edema is interstitial rather than in the smaller divisions of the bronchial tree. On examination by x-ray the lungs show signs of congestion.

*Treatment* consists of emergency measures to control the acute episode, and attempts to prevent further recurrences. Morphine sulfate in a dose of 15 mg. is given hypodermically to quiet the patient. If the peripheral veins are not already distended and if the extremities are not already tight with edema, blood can be shunted from the lungs to the extremities by the use of tourniquets. Rubber tubing can be used but blood pressure cuffs are preferable. The tourniquets are applied to the proximal portions of the extremities as close to the trunk as possible. They are inflated to a pressure midway between the systolic and diastolic arterial pressures and are left in place till the acute attack has subsided. Then they are removed one at a time so that the blood accumulated by the tourniquets is not restored to the general circulation too abruptly. If the veins are already distended because of a high venous pressure or if the subcutaneous tissues are tight with edema, tourniquets cause little pooling of blood in the extremities. Under these circumstances the rapid removal of 500 to 1000 cc. of blood by venesection may produce great improvement in the patient's condition. The administration of a high concentration of oxygen by the use of a Boothby mask or an oxygen tent may be helpful. If the patient has not been digitalized, rapid digitalization by the intramuscular or intravenous routes may be indicated. Recurrences are prevented by proper use of digitalis, rest, dietary restriction of sodium chloride and the persistent use of diuretics.

In the discussion of the treatment of the specific symptoms of cardiac failure we must not lose sight of the fact that we are treating a patient as well as a disease. The patient will be anxious about his own welfare and he will interpret any physiological disturbances in function as evidence of progressive heart disease. The counsel of an intelligent physician will aid greatly in giving him mental as well as physical rest.

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# CONGENITAL PATENT DUCTUS ARTERIOSUS. AN EVALUATION OF ITS SURGICAL TREATMENT

GEORGE E BURCH, M D , F A C P \*

SINCE the early description of the ductus arteriosus by Galen,<sup>1</sup> there has been, until several years ago, relatively little change in the management of patients with a persistence of the ductus. Treatment was entirely medical, emphasis being placed on restriction of activity and the subsequent management of congestive heart failure and bacterial endarteritis as major complications. A great advance in the treatment of this condition occurred in 1938 when Graybiel, Strieder and Boyer<sup>2</sup> reported the first attempt to ligate a patent ductus arteriosus despite the fact that the patient died. This attempt at least gave impetus to further trials at ligation. As early as 1907 Munro<sup>3</sup> developed an operative approach for ligation of a patent ductus and presented clinical evidence to prove the rational basis for such an operation, but his suggestion was ignored for thirty-one years. Success was finally achieved in 1939, when Gross and Hubbard<sup>4</sup> reported the first ligation of a patent ductus arteriosus followed by recovery.

Because of the striking benefit obtained by Gross and Hubbard and the impressive results following operation in the hands of others, there has developed a wave of enthusiastic interest in the surgical treatment of patent ductus arteriosus. This can be readily understood, since the development of a safe operative procedure to correct a persistent ductus arteriosus has made it possible to convert an irreversible type of heart disease into a reversible or curable one. These rapid developments have prompted an analysis of the surgical results to date in order to evaluate better the indications and contraindications for operation.

## PHYSIOLOGICAL CONSIDERATIONS

Eppinger, Burwell and Gross<sup>5, 6</sup> and Eppinger and Burwell<sup>7</sup> studied the circulation of the blood through the patent ductus arteriosus in man at operation and also in dogs. In these latter investigations a fistulous connection was made between the aorta and the pulmonary artery. The blood was observed to flow from the aorta to the pulmonary artery, as would be expected on the basis of the pressures in the two circulatory systems. Rarely was there any flow of blood in the

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From the Section on Internal Medicine, Ochsner Clinic and the Department of Medicine, Tulane University School of Medicine, New Orleans.

\* Associate Professor of Internal Medicine, Tulane University School of Medicine, Visiting Physician, Charity Hospital in New Orleans and Touro Infirmary, Consultant in Cardiovascular Diseases, Ochsner Clinic.

reverse direction, that is, from the pulmonary artery to the aorta. This explains the absence of cyanosis. In their patients, from 4 to 19 liters of blood per minute was found to enter directly from the aorta into the pulmonary artery. This represented from 45 to 75 per cent of all the blood leaving the left ventricle.

The blood entering the pulmonary artery returns to the left ventricle via the lungs without reaching the peripheral circulation. In order to compensate for the loss of blood in the periphery, the volume output from the left ventricle must increase. This occurs without much change in that of the right ventricle. The result is a considerable increase in the work of the left ventricle, left ventricular enlargement, strain and eventual failure. There is some increase in the work of the right ventricle, as it must circulate the added amount of blood entering the pulmonary artery from the aorta. Eppinger and his associates<sup>5</sup> found the left ventricle pumping four times the volume of blood expelled by the right ventricle. These effects on ventricular work explain the normal axis deviation or mild left axis deviation and the rare right axis deviation in the electrocardiogram. The patent ductus arteriosus is associated with many of the hemodynamic and other cardiophysiologic manifestations so well known in aortic regurgitation and arteriovenous aneurysm.

The *roentgenologic signs* observed by teleoroentgenography, fluoroscopy or roentgenokymography, easily explained on the basis of the disturbed physiologic condition already discussed are as follows:<sup>6,7</sup> (1) greatly increased excursions of the left ventricle, (2) increased pulsations of the pulmonary artery, (3) overfilling or engorgement of the pulmonary conus and pulmonary vessels, (4) increased pulsations of the bronchovascular structure, particularly prominent near the hilar regions, and (5) enlargement of the left ventricle.

The changes in hemodynamics also explain the typical "machine-like" murmur and the other murmurs so commonly heard in this anomaly. The former murmur is characteristic when properly located in the region of the pulmonary valve of the chest. Further details of changes in the dynamics of the circulation can be found in the papers of Eppinger and his associates. It is well to point out at this time that when the ductus is successfully ligated the circulation dramatically returns to normal within a short time, a matter of seconds to hours.<sup>8</sup>

It is beyond the scope of this paper to discuss the anatomy, embryology, method of closure and other physiologic phenomena associated with patent ductus arteriosus. The papers of Franklin,<sup>1</sup> Boyd,<sup>2</sup> Barclay et al.,<sup>3</sup> Noback and Relman,<sup>10</sup> Kennedy,<sup>11</sup> Kennedy and Clark,<sup>12</sup> and Jager and Wollenman<sup>13</sup> in addition to the standard textbooks may be consulted by those interested in these phases of the subject.

## RESULTS OF LIGATION OR EXCISION

Since the failure of Graybiel, Strieder and Boyer<sup>2</sup> in 1938 to ligate a patent ductus arteriosus with superimposed infection, there have been in the literature many reports on the surgical treatment of this anomaly. Gross and Hubbard<sup>4</sup> in 1939 reported the first successful ligation. Since then these authors and others have reported many surgical results at such a rapid rate that it is difficult to determine the chronologic order of publication, especially since several authors have written several reports on the same patients within a few months' interval. In spite of these facts an attempt has been made to list in chronological order of publication from most of the available reports the results of ligation of the patent ductus arteriosus (Tabulation). By this means at least an impression of the published results can be obtained. It must be remembered that there have been many unrecorded cases, especially fatal ones, which are less apt to be reported. Therefore, such statistics will indicate only the trend of the results of surgical treatment.

## ANALYSIS OF LITERATURE

In 1938 Graybiel, Strieder and Boyer<sup>2</sup> attempted to ligate a patent ductus arteriosus complicated by subacute bacterial endarteritis (*Streptococcus viridans*) but the patient died. Gross and Hubbard<sup>4</sup> in 1939 reported a successful ligation in a 7½-year-old girl who showed signs of impairment in growth and cardiac enlargement. Gross<sup>14</sup> reported his results in 4 patients one month later and at the same time described a surgical approach for the operation, three of the cases were new and the results were likewise successful.

Jones and his associates<sup>15</sup> reported during the next month their immediate results in 7 cases. All of these patients were apparently cured or greatly benefited. One, however, died thirty days later of an infection due to the hemolytic *Staphylococcus aureus*. These authors included an addendum to this same report in which they cited 6 more successful operations making a total of 13 cases with only 1 death. Several months later they<sup>16</sup> reported their results in 11 cases in more detail. It is a bit confusing from these articles to know which were the patients previously reported. The success of the operation is modified somewhat in the later report, since in 6 of the 11 patients a systolic murmur remained. Of course, a sufficient length of time must elapse before the results in such patients can be properly evaluated. Such overlapping of cases and variations in descriptions make an evaluation of the results in the literature difficult. Stephens,<sup>17</sup> in the discussion of the paper of Jones and his co-workers,<sup>18</sup> reported a death from infection on the third postoperative day. Gross, Emerson and Green<sup>18</sup> reported a case of successful ligation of the ductus but the patient is probably one previously reported by Gross.<sup>14</sup> Gross<sup>19</sup> summarized his



results in 4 cases in which the ductus was ligated without a single death

Touroff and Tuchman<sup>9</sup> reported a successful ligation in a 51-year-old woman with a patent ductus and superimposed endarteritis (*Streptococcus viridans*). This same patient had made a spontaneous recovery from endarteritis under medical treatment twelve and a half years before Gross,<sup>1</sup> summarizing his experience with ligation in 10 patients, reported 1 death from infection postoperatively, no improvement in 1 case and remarkable improvement in the remaining 8. Kerr<sup>22</sup> in the discussion of Gross's paper<sup>21</sup> cited 2 cases, a young girl who died from infection and a child who showed no improvement following ligation. In the latter case Kerr suggested the possibility of multiple cardiac lesions as the reason that complete cure was not effected by the operation.

Touroff and Vesell<sup>23</sup> reported a cure in a 29-year-old woman who had a patent ductus arteriosus with a superimposed subacute *Streptococcus viridans* endarteritis. These same writers<sup>24</sup> later reviewed their results with ligation in 4 patients with subacute *Streptococcus viridans* endarteritis superimposed upon a patent ductus arteriosus. One patient, apparently the one mentioned above,<sup>23</sup> was cured, 2 died of hemorrhage and the other continued to show bacteremia, as the duct was too short for excision and was only ligated. Gross<sup>25</sup> summarized his results again in 13 patients subjected to ligation of the ductus. One died of infection, 1 was not benefited and 11 were definitely improved or cured.

Gale and his co-workers<sup>26</sup> reported a successful ligation in a 19-year-old girl. Miangolarra and Hull<sup>27</sup> described a successful ligation in a 20-year-old woman and a death from hemorrhage in a 12-year-old boy. Castellano and co-workers<sup>28</sup> reported a case of a patent ductus arteriosus in which ligation resulted in cure. Gebauer and Nichol<sup>29</sup> ligated the ductus in three patients, the 39-year-old woman died of hemorrhage but the 11- and 14-year-old children recovered and were clinically improved. Bourne and his associates<sup>30</sup> ligated the ductus in a 23-year-old man with subacute bacterial endarteritis (*Streptococcus viridans* and *Haemophilus influenzae*) in whom the cultures remained positive although the patient was well sixteen months later. Ligation was also performed in a 19-year-old girl with subacute bacterial endarteritis (*Streptococcus viridans*), and she was well eleven months later. Sulfonamides were used in treating both of these patients. Bourne<sup>31</sup> again reported the same 19-year-old patient elsewhere. Shipiro and Keys<sup>32</sup> studied 23 of their patients with patent ductus and reviewed patients operated on by observers. A more detailed analysis is presented by these authors in a later paper (vide infra). Camas and Gonzalez Sabathie<sup>33</sup> presented the case of a 10-year-old boy who made an excellent recovery following ligation of a patent ductus.

## SUMMARY OF MOST OF CASE REPORTS IN LITERATURE ON LIGATION OF PATENT DUCTUS ARTERIOSUS TABULATED IN CHRONOLOGICAL ORDER OF PUBLICATION\*

Author	Date Published	Patients			Results					Remarks	
		Age	Sex	Cases	Cure	Imp	Not Cured	Deaths			
								Hem	Inf.		Others
Graybiel, Strieder & Boyer <sup>1</sup>	May 1938			1				1			SV
Gross & Hubbard <sup>4</sup>	Feb 1939	7½	F	1	1						
Gross <sup>14</sup>	Mar 1939			4	2	2					
Jones, Dolley & Bullock <sup>15</sup>	April 1939			13	11	1				1	Pt died of H Staph. aureus
Stephens <sup>17</sup>	April 1939	26	F	1						1	H Staph aureus
Gross, Emerson & Green <sup>18</sup>	Aug 1939	11	M	1	1						
Gross <sup>19</sup>	Sept 1939	7, 7 17, 11	3 F 1 M	4	4						
Bullock, Jones & Dolley <sup>16</sup>	Dec 1939	4-31	4 M 7 F	11	10					1	1 died of Staph aureus
Touroff & Tuchman <sup>20</sup>	June 1940	51	F	1	1						SV
Gross <sup>21</sup>	Oct 1940			10	8	1				1	1 died of Staph aureus
Kerr <sup>22</sup>	Oct 1940		F	2		1				1	1 died of Staph aureus
Touroff & Vesell <sup>23</sup>	Oct 1940	29	F	1	1						SV
Touroff & Vesell <sup>4</sup>	Oct 1940	24-63	4 F	4	1			1	2		SV in all
Gross <sup>25</sup>	Dec 1940			13	11			1		1	1 died of Staph aureus
Gale et al <sup>24</sup>	April 1941	19	F	1	1						
Miangolarn & Hull <sup>27</sup>	April 1941	12 20	M F	2	1				1		
Castellano et al <sup>28</sup>	April 1941			1	1						

[illegible]

been made to collect all cases which have been reported

1. *Staphylococcus aureus*  
 2. *Staphylococcus aureus*  
 3. *Staphylococcus aureus*  
 4. *Staphylococcus aureus*  
 5. *Staphylococcus aureus*  
 6. *Staphylococcus aureus*  
 7. *Staphylococcus aureus*  
 8. *Staphylococcus aureus*  
 9. *Staphylococcus aureus*  
 10. *Staphylococcus aureus*

Johnson and his associates<sup>34</sup> reported 7 patients in whom the ductus was ligated. One died of hemorrhage, one had subacute bacterial endarteritis (*Streptococcus viridans*) and died seven months after operation and in 5 the ligations were successful. Winn, Hughes and Sanders<sup>35</sup> ligated a ductus in a patient with subacute bacterial endarteritis (*Streptococcus viridans*) and supplemented this with sulfapyridine and heparin. One year later the patient was in excellent health. Touroff, Vesell and Chasnoff<sup>36</sup> reported their second patient with patent ductus arteriosus with subacute bacterial endarteritis (*Streptococcus viridans*) who was cured by ligation. Vedoya and his associates<sup>37</sup> described their results with ligation in 4 patients. One patient died at operation, 1 was benefited and in two the results were excellent. Nixon<sup>38</sup> reported a successful ligation in a 15-year-old girl. Touroff<sup>39</sup> reported 4 additional ligations in patients with a patent ductus with superimposed *Streptococcus viridans* endarteritis. This brought Touroff's personal series of patent ductus associated with endarteritis to 8. Since this report appeared, Touroff had had 2 additional patients suffering from patent ductus arteriosus complicated by infection who were cured by operation.

Dayton and Lindskog<sup>40</sup> reported a cure by ligation of another patent ductus arteriosus complicated by *Streptococcus viridans* endarteritis. Humphreys<sup>41</sup> reported 16 ligations, all results were excellent except for a stormy convalescence in two instances. However, one year later 1 patient died of an aneurysm that developed postoperatively in the ductus and another died of bacterial endarteritis two months following operation. Dolley and Jones<sup>42</sup> summarized their results again. In their series of 18 cases ranging in age from 4 to 31 years, ligation was accomplished without a single immediate operative death. One patient died several days later of a staphylococcic infection in the region of the ductus. In 4 other patients a murmur developed and in one of these a continuous murmur recurred. Keys and Shapiro<sup>43</sup> made another analysis of collected cases. These cases will be taken up in greater detail when their third and apparently most recent analysis is discussed.

Touroff<sup>44</sup> in his next report added 3 more cases of ligation of patent ductus arteriosus complicated by endarteritis, making a total of 11 cases, which formed the basis for his most recent report. Two patients died of hemorrhage, 6 recovered without the aid of chemotherapy, 3 continued to have positive blood cultures and 1 of these died eight months later. Harrington<sup>45</sup> reported a successful ligation in a patient with a superimposed subacute bacterial endarteritis (*Streptococcus viridans*), he has operated on 5 other patients with good results.

Shapiro and Keys<sup>46</sup> described the results of 140 ligations by 25 surgical teams, a great number of which were collected by personal correspondence with surgeons. The remainder were collected from the literature. Of these, 107 were uncomplicated and 33 were associated with a

superimposed bacterial endarteritis. Seven of the patients were from the author's series. Of the 107 uncomplicated cases, 81 were successful except for a distant short systolic murmur that remained in a few instances over the pulmonic area. In 14 the continuous murmur remained. In 6 death resulted from rupture of the duct, in 2 bacterial endarteritis developed after operation, in 1 case mediastinitis with death resulted, in 1 there was no duct to ligate (a direct anastomosis between the aorta and pulmonary artery was found so nothing was done), in 3 a vessel other than the duct was ligated (the aorta in one instance) and 2 of these died, and in 2 the diagnosis was mistaken. There was a total of 9 deaths in the 107 cases (the 2 with endarteritis after operation were not included), a mortality rate of 8.5 per cent.

Of the 33 patients operated upon in the presence of superimposed bacterial endarteritis, 20 seemed to have been completely cured clinically. Five patients died at operation of rupture of the duct and in 8 fever persisted in spite of operation. This gives an apparently favorable prognosis of more than 50 per cent in a disease with a previous mortality of almost 100 per cent. In the preceding table the reports which have been discussed are summarized in tabular form.

#### CLINICAL PICTURE

The clinical picture of patent ductus arteriosus may vary considerably in specific cases but in general the syndrome is fairly characteristic.<sup>19 21 47</sup> The most representative feature is a loud harsh *murmur* best heard over the region of the pulmonary valve. It is usually continuous with systolic exacerbations. The loud, snappy, second pulmonic heart sound heard with the murmur produces a "machine-like" effect. The systolic murmur is crescendo and the diastolic one is decrescendo. There usually is a definite systolic thrill and often a continuous one with systolic exacerbations. The murmurs and thrills may be best elicited with the subject leaning forward and the lungs emptied to a maximum. The murmurs and thrills are produced by the blood flowing from the aorta into the pulmonary artery. These manifestations vary in degree with the size and anatomic nature of the ductus. The patients will usually give a history of the presence of a murmur from birth or since their first physical examination.

These patients usually present no cyanosis, since aerated blood is entering the pulmonary circuit from the aorta. As the patient becomes older the increased burden on the heart begins to manifest itself by *cardiac enlargement*. After a time *congestive heart failure* develops and the manifestations of left and right ventricular decompensation will gradually appear and become progressively worse. If bacterial infection of the ductus develops, then there will be a picture of *bacterial endocarditis* with the embolic phenomena present mainly in the lungs. The *Streptococcus viridans* is the most common offending organism. There

may be a wide pulse pressure with an elevated systolic pressure and even a slightly lowered diastolic pressure. This may result in peripheral vascular signs similar to those of aortic regurgitation. These patients often show definite retardation of physical and mental growth frequently to the extent of seriously jeopardizing their efficiency.

The *electrocardiogram* is not characteristic. It may vary from normal to one showing serious myocardial disease. The electrical axis may be deviated to the left or right or may not be changed from the normal. The appearance of the electrocardiogram is beyond the scope of this discussion. It is not really necessary to list the various electrocardiographic changes that might be noted.

The *roentgenographic study* is of great diagnostic significance in recognizing this anomaly.<sup>6, 7, 10, 21, 47</sup> There is a definite enlargement of the pulmonary conus and the pulmonary artery and its branches. A "hilar dance" may be seen on fluoroscopic examination.<sup>8</sup> The bronchovascular markings are increased. The left and right ventricles will show varying degrees of enlargement depending upon the duration of the lesion. The left ventricle shows distinct excursions with each cardiac cycle, which suggests a large stroke volume. Congestion of the lungs and other signs of congestive failure may be detected when failure is present. Infarcts in the lungs will be noted if there is bacterial endarteritis with embolism. The reader is referred to standard textbooks and monographs on cardiac disease for further details of the clinical syndrome.

#### LIFE EXPECTANCY AND INCIDENCE

In the presence of patent ductus arteriosus the life expectancy in untreated cases has been variously stated but in general the findings are essentially the same. Of 92 patients studied by Abbott,<sup>4</sup> one-fourth died of bacterial endarteritis and an additional one-half died of slow or rapid heart failure. The average age at death in this group of 92 cases was 24 years. Gross and his associates<sup>18</sup> estimated that a child with a patent ductus has one chance in four to live a normal length of life, one chance in four to die of bacterial endarteritis and almost two chances in four that he will die of heart failure. Bullock and his co-workers<sup>16</sup> found in 80 cases reviewed by them that 11 (14 per cent) died as a result of the congenital lesion by the age of 14, by 30 one-half were dead, by 40, 71 per cent were dead and 2 lived to the age of 66 years. Eighteen patients (23 per cent) died of congestive heart failure, 5 (6 per cent) of rupture of the ductus, 42 (53 per cent) of bacterial endarteritis, and 4 (5 per cent) of an associated condition. Thus, 69 (86 per cent) died as a result of the lesion. In 5 the cause of death was not given and in 6 (7 per cent) death was attributed to unrelated causes. Shapiro and Keys<sup>40</sup> found from a review of the literature that 80 per cent of such patients eventually died of the cardiac lesion. Pa-

tients alive at 17 years of age average 35 years at death, 40 per cent dying of subacute bacterial endarteritis and most of the remainder of congestive heart failure. Wilson and Lubschez<sup>18</sup> found no deaths from congestive heart failure and bacterial endarteritis in 38 patients with uncomplicated patent ductus. There was one unexplained sudden death. Twenty-four were between 10 and 20 years, 12 between 20 and 30 years and 2 over 30 years of age.

The incidence of persistent ductus arteriosus varies with the series reported. Bullock and his associates<sup>16</sup> found 133 instances of congenital heart disease in 21,000 autopsies at Los Angeles County Hospital. Thirty-six of these were cases of patent ductus, 21 of which had other associated defects. Twenty died before the age of 9 months, 10 with uncomplicated patent ductus were less than 2 months old. Every patient died as a result of this lesion. Wilson and Lubschez<sup>18</sup> estimated that 1 to 2 per cent of cases of organic heart disease in the adult and 5 to 12 per cent in children are the result of congenital malformations. An analysis of 54,842 reported autopsies<sup>7</sup> revealed that congenital defects constituted 1.3 per cent of all cases, the reported incidences varying from 0.6 to 5.4 per cent. Of 152 patients with congenital cardiac malformations on whom autopsies were performed at the New York Nursery and Child's Hospital 10.5 per cent were cases of patent ductus arteriosus. Of the 54,842 autopsies 63 (0.11 per cent) of these patients had a patent ductus. Of the total congenital anomalies 10.3 per cent were patent ductus arteriosus. Keys and Shapiro<sup>13</sup> estimated that about 20,000 persons in the United States have a patent ductus arteriosus. About two thirds of them are females.

#### CAUSES OF FAILURE FOLLOWING LIGATION

Gross<sup>25</sup> attributes poor results of operation to (1) failure to find the ductus, (2) a ductus too short to ligate, (3) ligation of a wrong vessel (4) hemorrhage from the ductus, (5) incomplete obliteration of the ductus (6) associated cardiovascular abnormalities, (7) wound sepsis, (8) postoperative pneumonia as well as pulmonary embolism preoperatively. The nature of these causes of failure is obvious. Most of them are technical considerations whereas some will enter into the surgical problem as they do in any major surgical procedure in the thorax. Hemorrhage is particularly apt to occur in patients with superimposed bacterial endarteritis. The infection renders the ductus friable which results in rupture or cutting through of the ligature. With improvement in the operative procedure there will undoubtedly be fewer failures.

#### INDICATIONS FOR OPERATION

The indications for operation are not too definite at present but certain generally accepted concepts may be enumerated.

1 The surgical risk is still not good enough in average hands to recommend operation to all patients with patent ductus arteriosus. With further improvement of the operative technic such a recommendation may be made, especially in view of the morbidity and short duration of life associated with this defect.

2 Because of the high mortality rate in those patients with superimposed endarteritis who are not subjected to ligation and the greater than 50 per cent cure (*vide supra*) following ligation, the operation should be recommended when endarteritis is present.<sup>23</sup> The prerequisites for successful operation are (*a*) that the vegetations be confined to the ductus and (*b*) that the ductus be of sufficient length to permit excision. (These can be determined, at present, only at the time of operation.)

3 The operation should be performed in the presence of definite cardiac decompensation, especially if it is progressing.<sup>21</sup> (This would include patients who are showing signs of progressive failure, a large heart and serious disturbances in cardiac mechanism.)

4 Ligation of the ductus is indicated in patients showing definite retardation of physical and mental development.

#### COMMENT

It can be seen from the foregoing that the problem of patent ductus arteriosus is still unsettled. The mean mortality rate determined from the results of operations performed by many surgeons is about 8.5 per cent in cases of uninfected ducti. This does not represent the results that may be expected when a surgeon has had experience with only an occasional case or with many cases. Furthermore, as shown by Shapiro and Keys,<sup>46</sup> over 20 per cent of the patients operated on in 107 uncomplicated cases either died or were not benefited materially as far as the murmur was concerned.

There is no doubt that the life expectancy in persistent ductus arteriosus is considerably reduced. It is apparent too that most patients with an uncomplicated ductus are spectacularly benefited by ligation. It is also true, however, that these patients have only been followed four years after operation and only time will determine exactly what influence the operation has on the duration of life. Furthermore, in the presence of superimposed bacterial endarteritis the mortality rate for untreated cases is approximately 100 per cent, but ligation has reduced this to less than 50 per cent (*vide supra*) after a follow-up of about one year. Therefore, ligation should not only be recommended but urged if the patient has an associated endarteritis. The same is true in patients who have progressive cardiac damage and decompensation or patients with definite impairment of mental and physical development. One would nevertheless hesitate to recommend or assume the responsibilities for operation in a patient who has a patent ductus without any evi-



dence of embarrassment of health Dolley and Jones<sup>42</sup> found the operation easier to perform in children 4, 5, and 6 years old If this proves to be true, then the age of the patient will influence considerably the time at which operation should be recommended

It is conceivable that in the future the operation will usually be recommended as soon as a patent ductus is discovered No such recommendation can be made at this time with the operative mortality averaging 8.5 per cent and even being greater in average hands Until the surgeons have developed a procedure that is relatively safe and the results can be predicted preoperatively with a greater degree of certainty, the operation should be reserved for those special indications already listed

#### SUMMARY

Most of the available case reports in the literature on ligation of patent ductus arteriosus have been reviewed The average surgical mortality was found to be 8.5 per cent in uninfected ducti The rate varies considerably, however, depending on the surgeon and his experience (Tabulation)

The operation has been recommended for all patients with the anomaly if there is a superimposed bacterial endarteritis, more than 50 per cent of such patients have been cured by ligation of the ductus It is also strongly advised for patients with progressive cardiac failure and for patients with definite impairment of physical and mental growth.

Poor results following ligation may be attributed to (1) failure to find the ductus, (2) ligation of the wrong vessel (3) wound sepsis (4) hemorrhage, (5) a ductus too short for ligation (6) postoperative pneumonia (7) associated cardiovascular abnormalities and (8) incomplete obliteration of the ductus

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# THE MEDICAL TREATMENT OF PEPTIC ULCER

T GRIER MILLER, M.D., F.A.C.P.\*

## INTRODUCTION

THE management of a patient with simple uncomplicated peptic ulcer whether gastric or duodenal is fundamentally an art rather than a science. The etiology and pathogenesis of the affection are unknown, and so its therapy must be on an empirical rather than a rational basis. In spite of that, one might expect that an analysis of the results of treatment would have led finally to the acceptance of a regimen that had proved its worth. The natural history of the disease, however, is also uncertain and in consequence one is constantly confronted with the possibility that many of the cases in any particular series would have recovered without any therapy or as a result of some associated but unrecognized factor.

Under such circumstances it is not surprising that many programs for the treatment of ulcer have been evolved that each has its advocates and that, until the disturbance responsible for its occurrence and until its pathological physiology are determined, none of the procedures can be regarded as on a truly scientific basis. In this presentation, therefore, I shall merely outline the principles of therapy which, on the basis of results from a varied and reasonably extensive experience, I personally have finally adopted in the management of the average ulcer patient and also those that I regard as most satisfactory for its common medical complications.

## NATURAL TENDENCY TO HEALING

Clinical as well as autopsy data are available to indicate that many peptic ulcers heal naturally or at least without any intentional effort at treatment by either the patient or his physician. It is not uncommon for the ulcer patient to tell his doctor, on his first visit, that he has had similar symptoms previously and that in the course of weeks to months they subsided completely without any change in personal habits, environment or other routine of life and without any resort to medicinal or dietary therapy. The occurrence of gastric or duodenal perforation or hemorrhage in persons with ulcer who have had no previous symptoms, suggests that ulcerative lesions may develop and

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From the Gastro-Intestinal Section (Kinsey Thomas Foundation) of Medical Clinic University of Pennsylvania Hospital, Philadelphia.

\* Professor of Clinical Medicine School of Medicine, University of Pennsylvania Chief of Gastro-Intestinal Section (Kinsey-Thomas Foundation) of Medical Clinic University of Pennsylvania Hospital.

heal spontaneously. In further support of this hypothesis, duodenal and gastric scars are often found on roentgenologic examination in subjects who at no time had had any symptoms suggestive of ulcer. Also, the fact that at autopsy, as pointed out by Sturtevant and Shapiro, gastric ulcers and gastric ulcer scars predominate over duodenal ones, whereas, clinically and on roentgenologic examination, the duodenal lesions are found in excess, indicates either that many gastric ulcers are entirely overlooked clinically or, which is improbable, that many diagnosable duodenal ones heal without resultant scar formation.

In spite of the facts, however, that some peptic ulcers are symptomless and heal naturally, most of them produce a characteristic type of indigestion that tends to persist intermittently over long periods of time, and some of them lead to the development of serious complications. Furthermore, though satisfactory healing, with or without treatment, may take place, recurrences of activity are common. For these reasons it is necessary that in all diagnosed cases some definite form of medical management be instituted.

#### THE PSYCHIC FACTOR IN TREATMENT

The psychogenic factor in the etiology of peptic ulcer, as in many other affections of the digestive tract, is receiving a great deal of attention at the present time, due in part perhaps to the emphasis that is now being placed on psychosomatic medicine in general. It has been claimed, for instance, that disturbance of the emotional centers in the brain, acting through the hypothalamus and the autonomic nervous system, set up motor and secretory changes in the stomach, and also that by the same paths they sensitize its nervous mechanism and so lead to vasomotor reactions with ischemia (believed by some to be an important factor in the production of ulceration). Irrespective of the significance of such a theory as to the pathogenesis of ulcer, it is certainly true, with regard to its management, that when the ulcer patient puts himself in the hands of a competent, sympathetic and understanding physician, transfers to him his personal concern about his condition and cooperates with him in every detail of the management, the first great step toward recovery has been taken.

The ideal relationship between the doctor and his peptic ulcer patient does not develop spontaneously, although some physicians, by virtue of their personality, their reputation for competence and their ability quickly to understand and to adjust themselves to the patient's mental and emotional reactions, are able almost at once to secure his complete confidence and cooperation. More often this cordial and beneficial relationship develops only as a result of a conscious and meticulous effort on the part of the physician. That involves at least a careful, painstaking study of the case and the institution as promptly as possible of some form of management, however simple that may be.

The mere fact that the patient is made to feel from the beginning that his physician is interested, not only in him but also in his disease, and that his case is receiving personal study and treatment, is most important psychologically, and this is doubtless the explanation for the success of many varieties of therapy, whether rational or not and whether prescribed by a physician or a cultist.

An exhaustive investigation of the patient's disease condition, therefore, may be regarded not only as essential to the physician in order that he may make a correct diagnosis and outline an intelligent program of therapy, but also as an actual part of the management of the case. It should include, besides a carefully elicited and detailed account of all the complaints, whether strictly gastro-intestinal or not, and a meticulous examination of the entire body, at least the following special studies: a gastric analysis, a complete roentgenologic study of the digestive tract, an inspection of the feces, especially for blood, and sometimes, if the lesion is in the stomach, a gastroscopic investigation. If also, at the first visit, the patient is put on some simple dietary program, often only frequent feedings of a nonirritating diet, his thorough cooperation usually will have been secured by the time the diagnostic procedures have been completed and indeed his symptoms may, even before that time, have entirely disappeared. Even so, however, although no additional specific therapy may be required, the patient should, at least for psychological reasons, be kept under general observation and re-examined by a roentgenologist from time to time until all objective signs of activity have disappeared.

#### INITIAL MANAGEMENT OF THE AVERAGE CASE

For the sake of simplicity I shall now outline my ideas regarding the more specific aspects of peptic ulcer therapy dealing mainly with the average case that can be managed on an ambulatory basis, but also briefly with the more severe and the complicated cases that require hospitalization and more carefully controlled supervision.

Every patient suspected of having an ulceration of the stomach or duodenum unless it is contraindicated by a complication should have a prompt roentgenologic examination for exact diagnosis, and the treatment should be based in the main on the observations so made together with the history of the case. The physical examination and the gastric analysis are of secondary importance, and unless tenderness and rigidity or blood in the gastric contents are found, usually do not influence the type of therapy. In the average case without a complication, and even irrespective of the degree of discomfort, an ambulatory program may safely be given a short trial. It should include primarily measures designed to relieve discomfort or pain, to put the patient at ease mentally and physically, and to supply him with a diet adequate in all respects.

In some instances, even when the roentgen study has been essentially negative or at least shows no typical defect, the history may be so suggestive as to justify the diagnosis and a period of treatment, and always, irrespective of the patient's story, when an ulcer crater, either gastric or duodenal, with indirect signs of activity, is demonstrated roentgenologically, a detailed program of therapy should be outlined and insisted upon. This should be presented clearly and forcefully from the very beginning, with emphasis on the points that the patient has a chronic disease, that, though the symptoms may clear up readily, recurrences are common, that the lesion may last a long while after the symptoms have disappeared, even after the roentgen ray shows no further evidence of the ulcer, and that throughout his life he must insofar as possible avoid undue physical and mental fatigue, emotional crises and infections. It is also worthwhile, I think, to stress the facts that we do not know the exact cause of the disease, that no special medicinal preparation has been proved of value in its amelioration and that the ultimate result depends largely on the patient's cooperation in a regimen that involves various alterations in his habits of life.

1. Relief from Pain—Relief from discomfort or pain, whether mild and of a very transient nature or severe and more or less continuous with exacerbations when the stomach is empty, is the first essential of treatment and is ordinarily obtainable merely by the proper use of a bland, nonirritating diet. A mixture of milk and cream has proved its value over a long period of time and may be depended on entirely for the first few days, though I have usually obtained equally satisfactory results by including gelatin preparations, creamed soups, pureed vegetables, noncellulose-containing cereals, plain crackers with butter, cream cheese or jelly, eggs and simple desserts. These substances, however, to be effective in the relief of pain must be administered in small quantities and at frequent intervals, usually every two hours throughout the day, sometimes hourly, and occasionally even during the night. Rarely have I found it necessary in the ordinary case to give any drugs, though at times an alkaline mixture may be required for the first day or two. My experience with the antispasmodics has been very disappointing. Sedatives, such as the barbiturates, however, are frequently of great value, and should be used freely until the patient is adjusted to his new regimen of life.

When the patient becomes entirely comfortable throughout the twenty-four hours, which may be within a few days or only after a week or more, the intervals between feedings may be prolonged, usually so that he gets only six feedings a day, three at his regular meal-times with an intermediate one in the midmorning, in the midafternoon and at bedtime. Such a dietary program should be continued for three or four weeks (only two weeks in the case of a gastric ulcer) and then the patient should have a second roentgen examination.



2. Relief from Physical, Mental and Emotional Strain—Meantime during the preliminary period of treatment and perhaps most important from the viewpoint of ultimate recovery the routine of the patient's life should be so altered as to relieve him of all physical mental and emotional strain. The need for physical relaxation is fully appreciated in connection with all types of acute and chronic illness, but in spite of the emphasis that has been placed on it by all authors, it is not so well understood that mental anxiety and emotional stresses of every kind interfere equally with the healing of peptic ulcer. Since, as already stated, it has been demonstrated that mental reactions, including the emotions, directly affect certain gastric and intestinal functions, one has scientific justification for focusing attention on these factors. Anyway, every experienced physician knows that peptic ulcer develops most readily in persons who are highly keyed nervously, are intense, meticulous and worrisome, often sleepless easily fatigued and subject to emotional crises, also, that when the patient with an ulcer goes on a vacation, relaxes in his work or suddenly is able to resolve his business or domestic problems he begins to improve. On this purely empirical basis it is clear that freedom from emotional stress and mental tension is always indicated as a therapeutic procedure.

The accomplishment of such an alteration in the patient's way of life is often the most difficult aspect of the therapy, and yet the wise counsellor can sometimes bring it about merely by a frank explanation of the situation or by outlining in detail and firmly insisting on, a less strenuous attitude in the patient's business social and domestic relationships. Only rarely, if the physician himself understands the situation and has the necessary patience and ingenuity need he seek the assistance of a psychiatrist. In some instances, however, that is highly important.

3 Adequate Nutrition—Finally, among the fundamentals of treatment for the average case of peptic ulcer, is that of supplying him with an adequate diet, including the necessary vitamins and minerals. Although incidentally an improvement in the nutrition of the patient, as indicated by some gain in weight is usually accomplished by his frequent feedings the concentrated food substances that are prescribed and his freedom from nervous strain, already discussed this is not ordinarily regarded as a primary aim of the treatment. I believe it should be. I believe also that a mere gain in weight is not enough that may occur in the absence of a sufficiency of vitamins, perhaps also of minerals. The Sippy diet is known to be deficient in thiamine and ascorbic acid and yet patients may gain weight on it. This is a special reason for including additional food substances, such as the green vegetables and fruit juices even meats, reasonably early in the management or at least for adding some of the synthetic vitamins.

We have long appreciated that a certain constitutional type of in

dividual is most prone to ulcer formation the thin, hungry-looking, lantern-jawed, gastric-hyperacid type. Heredity has been assumed to be the important factor in the production of this constitutional type, but may it not be that heredity, like family influences, is effective mainly in that it determines certain food habits, a worrisome disposition and a sensitive, vagotonic gastro-intestinal tract? If so, it is not fair to say that we can do nothing about constitutional and hereditary influences, because, if we are patient, specific in our directions and forceful enough, we often can change the food habits, sometimes alter the mental reactions and, at least to some extent, control the secretory and motor disturbances of the stomach. At any rate, by such means, we not infrequently can greatly improve the nutrition of the subject, and in so doing it may be that we are approaching the matter of treatment in a truly rational way.

Data are rapidly accumulating to show that experimental wounds heal best when the nutrition is adequate, especially when the food contains an excess of proteins and vitamins, and that many skin and mucous membrane lesions disappear most readily when certain vitamins are administered. One need cite only the results in the typical lesions of pellagra in support of this contention. Furthermore, the modern treatment of the bleeding peptic ulcer (the Meulengracht program), which involves the prompt administration of an adequate diet, brings about healing far more readily than the older starvation regimen. One wonders, therefore, if the success of many of the modern treatments of simple ulcer is not due more largely to the fact that they include an adequate diet than to the fact that they happen to neutralize the gastric acidity, to coat the stomach wall, or to eliminate the harmful effects of tobacco, of certain endocrine disturbances, or of distant focal infection.

The fundamental points then that I wish particularly to emphasize in the treatment of the average uncomplicated and ambulatory ulcer patient are (1) that he be relieved of his discomfort, (2) that he secure freedom from physical, mental and emotional strain, and (3) that he get an adequate diet, with special reference to its protein, vitamin and mineral content.

#### ADDITIONAL POINTS IN THE MANAGEMENT OF THE AVERAGE CASE

Other factors commonly mentioned in connection with the etiology of peptic ulcer, however, deserve more specific consideration from the viewpoint of therapy. Although I do not regard any of these as of primary importance, each has a bearing on one or more of the therapeutic principles already discussed and its neglect may seriously retard ulcer healing.

1 **Gastric Acidity**—It is generally believed that the acid character of the stomach contents is a factor in the production of peptic ulcer,

chiefly because such a lesion does not develop in the achlorhydric stomach and because a hyperacidity is frequently found in association with ulcer, especially in the patient with a duodenal lesion. On the other hand, many subjects of hyperacidity never develop an ulcer and some believe that when a hyperchlorhydria does occur in the ulcer patient it is a secondary phenomenon. In any event, it does not follow that a peptic ulcer cannot heal when the gastric contents are acid, which is their normal reaction. It would be an unusual phenomenon in nature to require that a normally physiologic state be radically altered in order to bring about recovery from a diseased condition.

Clinically, as a matter of fact, we do know that peptic ulcer can heal in the presence of an acid reaction of the stomach contents, since this often occurs spontaneously and also when the ulcer is under a program of treatment that includes no measures designed completely to neutralize the gastric acidity. Indeed, it has been shown by Wosika and Emery<sup>1</sup> that, even when the Sippy program, including alkalies, is strictly enforced, the free acidity is reduced on the average only two clinical units below that obtained by the food alone. My experience also indicates that the ordinary regimen, including alkalies, does not usually bring about a complete neutralization of the gastric acidity. Furthermore, as Karr and Abbott have shown, unless the alkalies are given in very large dosage they tend to increase gastric evacuation, thus removing the food material that in itself is nature's neutralizing agent. The alkalies, therefore, tend to counterbalance the advantages of the addition of extra cream to the milk in the Sippy program, said to be due to its slowing up of gastric evacuation (presumably by stimulating the elaboration of enterogastrone).

Some reduction in the degree of the acidity of the gastric contents, however, does seem desirable in the management of peptic ulcer and this doubtless is the reason that the patient often instinctively develops the habit of taking extra feedings. Nature seems to indicate what he needs, since the characteristic pain is gnawing or that of hunger. Under normal conditions the acidity of the stomach contents rises and falls throughout the day, the fall occurring chiefly as a result of the intake of food, some food substances being more effective in this respect than others. It would seem reasonable therefore if one wishes to keep the acidity at a lower level to employ nature's own method rather than the use of alkalies, selecting however, the most effective foods and administering them at sufficiently frequent intervals to maintain comfort. After all our habit of eating only three times a day is artificial, it is by no means the custom in all countries.

The antacids, however, are sometimes helpful in the management of certain very active cases of ulcer, those with an unusually high acidity in order quickly to bring the pain under control, but I have

rarely found it necessary to continue their use for more than a few days. When employed over longer periods, beyond the time that food alone will control the pain, I have not found that they speed the healing process or tend to prevent ultimately a recurrence of activity. Furthermore, it has been shown that secondarily they actually tend to increase the gastric acidity and to interfere with the appetite—even in some instances to produce an alkalosis and renal stones. I have encountered patients who had been on an ulcer program for a long time, including alkalis, and who were discouraged, losing weight, having difficulty in taking their prescribed food and complaining of headache—all of these phenomena disappearing soon after the discontinuance of the alkaline medication and without other change in the regimen. Sometimes this has occurred when no alkalosis could be demonstrated chemically.

If the antacids are to be used at all, I prefer aluminum trisilicate or magnesium hydroxide, or even better a combination of these preparations, such as *gelusil*, which is a buffer substance and not a true alkali. Essentially, however, it seems to me unphysiologic markedly to disturb the acid character of the gastric contents, which plays such an important role in peptic digestion and the destruction of bacteria in the stomach and which influences both the secretory and motor functions of the intestines.

Unfortunately, no exact data on comparable groups of cases treated continuously with and without alkalis are available, but Dick and Eisele<sup>2</sup> have recently reported that, in forty-one cases treated by milk and cream feedings at hourly intervals and without either alkalis or night aspirations, the mean time of crater disappearance, as demonstrated by roentgen examination, occurred in 86 per cent within seventy-five days, in half of them within thirty days. Furthermore, only very occasionally have we in our clinic during the past twelve years used any neutralizing medication beyond the first week, and yet our results, I believe, have been at least as good, perhaps better, than previously when we followed a program that included the free use of the alkalis throughout the period of ulcer activity.

2. *Infection*—It is not obvious clinically that peptic ulcer develops as the result of either acute or chronic infection, or even in relation to focal infection, and yet a recurrence of activity not infrequently has been observed to follow an acute infection, especially of the upper respiratory tract, and sometimes improvement has followed the eradication of a focal infection. One naturally wonders if such infection does not act by undermining the general health and resistance of the patient, rather than as a specific factor. In any event, from the viewpoint of management, it would seem clear, as in the presence of any disease condition, that all focal infection should be carefully searched for and eliminated and that every person with an ulcer, active or inac-

tive, should meticulously avoid insofar as possible contact with those suffering from an acute respiratory infection and should take extra precautions, when afflicted with a general infection of any kind, to assure himself a carefully selected and nutritious diet, taken at frequent intervals

3 Hormonal Influences—Recent investigations, chiefly of an experimental nature, seem to be preparing the way for a therapeutic trial of various hormones in peptic ulcer. The work of Ivy, Quigley and their associates with enterogastrone, which in the presence of fats is liberated by the intestinal mucosa, is particularly encouraging. They have showed that it depresses both gastric secretion and motility. Likewise Sandweiss and his associates<sup>3</sup> have isolated from human urine a hormone that, through some primary action in the intestine, brings about changes in the gastric mucosa that benefit the healing of experimental ulcer in the dog. Although this substance also is a gastric secretory depressant, they believe that its significant effect on ulcer healing is due to stimulation of fibroblastic and epithelial proliferation and the formation of new blood vessels in the stomach wall. They claim encouraging results in a series of sixty-three chronic duodenal ulcer cases in the human. As yet, however, neither of these substances has been given a sufficient clinical trial to justify its further discussion in this presentation.

4 Personal Habits—The personal habits of the ulcer subject are more amenable to regulation, and doubtless for this reason have received a great deal of attention from the profession. It is probable, however, that their importance depends on whether or not they are prejudicial to the patient's general health. As in any disease condition, particularly when the nutrition is disturbed, every effort should be made to avoid physical fatigue, to secure some outdoor recreation, to get plenty of sleep and to be temperate in the use of stimulants.

Because of the location of the lesion, it is particularly important in the ulcer case that all food and drink that may be irritating either mechanically or chemically should be avoided. One should therefore forbid the use of the *coarser food substances*, those that cannot be thoroughly macerated, even liquefied in the mouth, because of their possible mechanical irritation, and also forbid the use of the highly acid foods and the condiments, because of their chemical irritation. In the proscribed list of foods should be placed the more fibrous vegetables, raw fruits except perhaps orange juice, all fruit seeds, skins and pulp, salads, whole wheat breads and nuts. I have observed a severe reaction, even with hemorrhage, in a previously quiescent ulcer after the ingestion of peanuts, presumably due to the lodgment in the ulcer crater of small pieces that cause chemical irritation, such as occurs in the lung after their inhalation.

Whether or not *tea* should be allowed is still an open question, but personally after the first week or two in a patient who is doing well I

have not hesitated to include it, particularly because of its content of protein and vitamins, and without obvious disturbance. Although the meats do tend to increase the gastric secretion, at the same time they neutralize the acid readily and also increase the patient's desire for other foods.

In this connection it is most important that the eating habits be regulated—that the patient eat deliberately and only when he is mentally at ease, that his food be thoroughly chewed, and that he expectorate such particles as cannot be liquefied in the mouth. This suggests also that he should have good dentures and make good use of them.

The use of *tobacco* has caused considerable controversy, and the general opinion is that smoking should be strictly forbidden. Certain evidence suggests that it increases the acid secretion of the stomach, but whether or not that occurs in the human subject on an adequate diet has not been determined. To argue that the recent increase in the sale of cigarettes is responsible for the present increase in the incidence of ulcer is hardly justifiable, in view of the many other factors that may be involved. Nicotine does, however, increase vasomotor tone, a possible factor in ulcer production, and on that basis it would seem wise in the ulcer case to restrict its use. On the same basis, however, *alcohol* might be advised, since it relaxes the tension in blood vessels. In spite of this pharmacological observation, there are good clinical reasons for avoiding the use of alcoholic beverages. Most clinicians have observed flare-ups in a quiescent ulcer after the ingestion of alcohol, probably due to its directly irritating qualities. Also, it may have an injurious effect because it leads to careless eating habits, especially to rapid eating, insufficient chewing and an indiscriminate selection of food substances.

#### LATER MANAGEMENT OF THE AVERAGE CASE

After two weeks in every case of demonstrated gastric ulcer, and after four to six weeks in that of a duodenal ulcer, another careful roentgenologic examination should be made. In the former instance, unless by that time the crater is obviously smaller and the patient's symptoms have entirely disappeared, he should be hospitalized for a more intensive program of diagnosis and therapy or he should at once be subjected to surgical intervention, because of the possibility that the lesion is malignant. Operative interference is particularly indicated if the pylorus or greater curvature of the stomach is involved, if the defect, after two weeks, is not obviously smaller, and if a gastroscopic investigation is not convincingly in favor of the lesion being benign. At times, even when the middle third of the lesser curvature is involved, where malignant lesions are much less common, further medical treatment is not justified. In the case of a duodenal ulcer, however, even if no decrease in the size of the crater can be shown, further conservative

therapy is usually safe, but if, after a month, the symptoms have not entirely cleared up I believe it is best at least to hospitalize the patient for a more strict program of treatment.

Consequently, in the case of a gastric ulcer that is objectively showing a favorable response to ambulatory therapy and in the case of the usual duodenal ulcer that is symptom-free after two to four weeks, a continuation of ambulatory management is justified. This need not be altered markedly from that already described, but in most instances the restrictions on the diet may be relaxed somewhat, the softer green vegetables no longer need be puréed, some of the less acid fruits, uncooked, may be permitted, and, if night feedings have been necessary for the relief of discomfort, they may be omitted. Intermediate feedings during the day, however, should be maintained for another month or two, depending on the patient's general progress and his response to their omission from time to time. The other items of therapy, especially freedom from mental and emotional strain, a fully adequate diet, abstinence from alcohol and the excessive use of tobacco, and meticulous care as to the habits of eating, should be maintained indefinitely. Eventually also, after further roentgen investigation and the disappearance of all signs of activity, the intermediate feedings may be entirely omitted, but the patient should be ready to go back to them immediately if subjected to any special strain in life, to physical fatigue or to infection of any kind. Only by such a prolonged regimen of prophylactic therapy may one expect to avoid a recurrence of ulcer activity.

Subsequently, for at least two years, and no matter how well the patient seems to be, he should report to his physician from time to time for a review of his progress and, on any recurrence of ulcer symptoms, he should have another roentgenologic examination.

#### MANAGEMENT OF THE MORE SEVERE CASES

In the foregoing paragraphs I have referred to occasional developments in the average ambulatory case that demand a more radical form of therapy—the failure of certain gastric lesions quickly to show signs of healing and the persistence of symptoms in certain duodenal cases. In addition, some cases present such severe symptoms from the beginning as to indicate a need for continuous observation and some although they seem to be doing well for a time, develop a recurrence of symptoms suggesting reactivation. In all these cases as well as in those with complications, to be discussed later, hospitalization is clearly indicated. Except in those with a definite complication and in those that demand prompt surgical interference because of the possibility of the complication of malignancy a strict medical program is required.

Such a regimen should include bed rest, a carefully supervised dietary—in some instances limiting it to milk and cream feedings, the appli-

cation of moist heat to the epigastrium and the use of antispasmodics for the relief of pyloric spasm, the administration of mild sedatives and the inauguration of a deliberate plan to free the patient of anxiety, fear, or whatever psychological disturbance may be present. In some instances, even the use for a short time of alkalis or at least of antacids of some kind may be indicated. Some authors advocate in the more resistant cases a continuous drip of aluminum hydroxide, even throughout the night, but I have not found that procedure of any special value. I shall not discuss the details of such hospital management further at this time, since my interest here is primarily in the average ambulatory case, but would point out that, on such a program, in many of the cases the severity of the symptoms will quickly subside, so that subsequently they can be managed as ambulatory cases. When they do not do so, they are regarded as refractory and so are commonly regarded as candidates for surgical intervention.

#### MANAGEMENT OF THE COMPLICATIONS

The clinically important complications of peptic ulcer are perforation, hemorrhage, stenosis and malignant degeneration. Of these, perforation is primarily surgical, the internist having no immediate responsibility beyond making the diagnosis promptly and putting the patient in the hands of a competent surgeon, the subsequent medical management deserving no attention in this presentation.

I. Hemorrhage—Hemorrhage, the second complication, however, is as strictly a medical problem, in my opinion, as is perforation a surgical one. The results from the medical management of bleeding peptic ulcer are now so satisfactory that only in the rarest instances is there any justification for an immediate surgical consultation, and that when some additional complication is suspected. Later, when the bleeding has ceased, operation is frequently indicated, especially if more than one hemorrhage has occurred. This aspect of the situation also I will not discuss further in this paper.

The prompt-feeding regimen for the treatment of bleeding ulcer, advocated by Lenhart, by Andresen and, in 1934, by Meulengracht,<sup>4</sup> has been adopted in many clinics throughout this country. The results, as tabulated in a recent report by Rasberry and Miller,<sup>5</sup> are far better than have been published for any single group of cases treated by other methods. In 1938 Miller and Elsom<sup>6</sup> assembled data on 5843 reported cases of gross bleeding treated by the previously accepted starvation program that showed a mortality of 8.7 per cent, several groups as high as 15 to 25 per cent. In a collected series of 383 cases treated surgically they found a mortality of 28 per cent, the lowest being 5.9 (Finsterer, who operated on all his cases early, irrespective of the degree of hemorrhage). Rasberry and Miller, on the other hand, found in a series of 2111 promptly fed cases collected from the literature, and including



seventy-five of their own, that the total mortality was only 4 per cent, and on further analysis discovered that many of the cases in which death occurred should be eliminated, because of coincident perforation pneumonia, carcinoma or cardiac disease, or because the patients were moribund on admission to the hospital and could not have been saved by any type of therapy. Eliminating such cases they got a mortality of 1.9 per cent for the total series.

It is inevitable that death will occur in a few cases of bleeding ulcer, usually those in older people who have a large, open, sclerotic vessel in the base of the ulcer, but, on the basis of the analysis referred to, it would seem that the number is exceedingly small surely far less than would result if surgery were employed in all of the severe cases. Furthermore it would seem possible to explain the lessened mortality in the promptly fed cases, as compared with those treated by starvation, on the basis of an adequate diet, which maintains the nutrition of the patient throughout the period of shock of a sufficient fluid intake, which also combats shock, and of freedom from anxiety, which has been a marked characteristic of all the cases treated by prompt feeding. An additional factor in my opinion is the fact that when the patient is fed it is rarely necessary to use morphine, which has a tendency to keep the gastric and duodenal musculature relaxed. Whatever the explanation, the present results seem definitely to justify the so-called Meulengracht regimen.

This program involves immediate feeding even in the midst of the hemorrhage and persistence in the feeding irrespective of developments. The food should be given at least six times a day. Although Meulengracht gave ground meats as well as vegetable purées, bread and butter, oatmeal and tea, the principle of his program was the immediate feeding and not a specific sort of diet. We have not felt that the type of diet need be different from that we ordinarily use in ulcer cases, and some authors have reported using only milk and cream. Witts<sup>2</sup> has emphasized the importance of including an adequate amount of fluid by mouth and of giving transfusions as indicated by the general condition of the patient. We have also done those things and have in addition insisted that no morphine be administered, using instead sodium luminal as required for the comfort of the patient.

On such a program the bleeding may continue for some days but since the patient is comfortable, is not in shock, and the blood loss can be cared for by transfusions, one should not lose confidence in the regimen. Eventually in almost all cases (all but one in our series of seventy-five) the hemorrhage eventually ceases. Several deaths have been reported when the program was stopped because of the continued bleeding and the patient put on starvation. Such instances of course should not be regarded as deaths on the feeding program.

2 Stenosis.—Pyloric stenosis, if of permanent organic nature is a

complication that must be handled surgically. In many instances, however, the obstruction is due to some medically remediable condition, such as edema or spasm. The patient must be kept under observation at least until the nature of the obstructing lesion is determined. In all of the cases, therefore, that show obstruction by the roentgen ray, the patient should be hospitalized and put on a simple medical program designed to relieve gastric retention and to promote evacuation through the pylorus. This of course necessitates the use of a fluid diet, administered in small amounts and at frequent intervals, and some muscle relaxant, such as belladonna, novatropine, or syntropan. Hot applications over the epigastrium at times seem very helpful. Also, because of the possibility that the obstruction is due to edema rather than spasm and that the edema is dependent on hypoproteinemia, a determination of the blood plasma protein concentration should be made at once. If the figure is low, blood transfusions or plasma injections are indicated. Ideally, one would like to be able to pass a tube through the pylorus to the jejunum and give protein feedings, but usually that is impossible because of the degree of the stenosing lesion.

If the edema is on an inflammatory basis it often is helpful to intubate the stomach, leaving the tube in place, and to aspirate completely the gastric contents about two hours after each feeding. In this way the stomach is never allowed to become distended, fighting peristalsis is avoided, and at the same time, some nourishment usually gets through to the bowel where it can be absorbed. As a matter of fact, such a procedure allows one to judge from time to time to what extent, if any, the obstruction is subsiding. It often subsides completely, and then the patient can be managed in the usual way.

**3 Malignancy**—The complication of malignant degeneration in a peptic ulcer does not concern us fundamentally in this presentation, since the mere suspicion of such a change is always an indication for prompt surgical removal of the affected area. The only point that I need emphasize, therefore, is that no form of medical treatment is justified once the diagnosis of malignancy has been made or even is suspected. Fortunately, however, only gastric ulcers become malignant and a relatively small percentage of them, perhaps not more than 5 to 10 per cent. Palmer<sup>8</sup> doubts if any peptic ulcer, primarily benign, ever develops this complication, believing that the malignant ones are so from the beginning.

In any event, malignant ulcer of the stomach, with roentgenologic signs that cannot be differentiated from those of a benign lesion, does occur, and so in treating every gastric ulcerative lesion, the possibility of malignancy must be borne in mind. It is for this reason that the management of the gastric ulcer must be different from that of the duodenal one. Every such gastric case should be re-examined roentgenologically after two or three weeks and, unless all the indications

are then favorable, the patient should be hospitalized for another short period of medical therapy, on a stricter basis, and for a gastroscopic examination. Unless the latter investigation and a third roentgen study clearly suggest that the lesion is benign, he should be subjected to surgery. In any event, he should have other roentgen studies from time to time, and in some instances additional gastroscopic investigations, until the lesion has healed.

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# FUNCTIONAL DISTURBANCES OF THE ALIMENTARY TRACT

WALTER LINCOLN PALMER, M D , Ph D , F A C P \*

PERHAPS the most frequent complaints encountered by the general practitioner are those arising from functional disorders of the digestive system. These may be localized to certain sections of the alimentary tract, but Alvarez<sup>1</sup> has very properly pointed out that there is usually an underlying hyperirritability of the entire digestive tract, and as a rule a hypersensitive individual as well. None of the diagnostic terminologies used to describe these symptoms are entirely satisfactory, but on the other hand any name suffices if its limitations and connotations are properly understood. Some of the more frequent and more or less synonymous terms are nervous indigestion, spastic colitis, mucous colitis, functional colitis, irritable colon, irritable bowel, unstable or unhappy bowel or colon. White, Cobb and Jones<sup>2</sup> prefer the designation mucous colitis, pointing out that the syndrome was described in detail with great accuracy by Da Costa in 1871 and also that the original meaning of the word colitis was "disorder of the colon" rather than "inflammation." The monograph published by these workers in 1939 is a classic.

## DIAGNOSIS

The symptoms of gastro-intestinal irritability are numerous and quite varied both in type and in severity. One may list belching, heart burn, bloating, abdominal distention, abdominal soreness, pain, anorexia, constipation and diarrhea as the more frequent complaints. Unfortunately, they are not pathognomonic of simple hyperirritability. Frequently such symptoms are the manifestation of a disturbed mental state or of organic disease outside of the digestive tract such as thyrotoxicosis or pulmonary tuberculosis, more frequently perhaps they serve to mask the presence of intra-abdominal lesions such as carcinoma. Consequently care should be taken to note symptoms not compatible with a functional disturbance and efforts should be made to exclude organic disease. The armed services have learned the importance of routine fluoroscopy of the chest, first demonstrated in civilian medicine.<sup>3, 4</sup> There is evidence that in time patients with dyspeptic complaints will receive routinely not only a fluoroscopy of the chest, but also of the esophagus, stomach and intestine. This will be a great forward step.

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From The Frank Billings Medical Clinic, Department of Medicine, University of Chicago, Chicago

\* Professor of Medicine, School of Medicine, University of Chicago, Attending Physician, Albert Merritt Billings Hospital

**Gastro-intestinal Discomfort and Pain**—In spite of the fact that there is no pathognomonic sign of hyperirritability of the digestive tract there is nevertheless a quite definite syndrome—a group of symptoms, certain physical findings, and a disturbance of bowel function, more or less characterizing the condition. For instance, belching while it occurs in normal individuals and in patients with various diseases, is usually a functional disturbance. Abnormal belching as a rule means abdominal discomfort which the patient attempts to relieve by swallowing and regurgitating air. A cure is best effected by explanation of the mechanism and relief of the discomfort which led to the formation of the habit.

This discomfort is rather typical of hyperirritability of the bowel. It tends to appear while eating or immediately after eating. If present before eating it may be aggravated by food taking or it may be relieved thereby, thus simulating peptic ulcer. The sensation is often one of distention—a feeling as though an enormous meal had been eaten whereas in reality only a small amount has been taken. The patient may have come to the table hungry and found that a few mouthfuls sufficed, or a regular meal may have been consumed to be followed not by a feeling of satiety but of acute discomfort and abdominal soreness, an unpleasant awareness of the abdomen. The localization of the distress is variable, frequently it is generalized, often it is upper or lower abdominal; sometimes it is localized to one of the lower quadrants. The patient attributes the discomfort to 'gas' or a "pocket of gas" which seems logical to him for it may be relieved temporarily by belching, by the passage of flatus or by rumbling and gurgling in the abdomen.

When the distress is more intense it tends to more precise localization in the lower abdomen and is interpreted by the patient as pain often shifting from one point to another but frequently persisting tenaciously in one spot. When constant the pain is a continued acute soreness or a more severe intermittent cramplike pain. The relationship to a bowel movement may be significant in that usually the pain is relieved thereby. There are cases however in which defecation precipitates pain. These abdominal sensations all seem to arise from a lowering of the visceral pain threshold perhaps from a true "soreness" with spasm and perverted muscular contractions. The cramps induced by a defecation contraction seem obviously attributable to spasm in the colon. Heartburn has been shown to be related to peristalsis and spasm in the lower esophagus.<sup>9</sup> Similarly substernal tightness, fullness and discomfort on swallowing may be related to spasm in the upper part of the esophagus. Loss of appetite and hunger may be related in part to a cessation of the normal contractions of the resting stomach and intestines, while nausea seems attributable to reverse peristalsis and a reversal of the normal gradient.<sup>2</sup> These phenomena are frequent

usually transitory and only rarely lead to vomiting or to loss of weight

**Physical Findings**—The physical examination usually discloses some tenderness of the colon on deep palpation. As a rule this is most noticeable in the left lower quadrant where the lower descending colon and the sigmoid may be rolled under the palpating fingers as a tender contracted tube. A loop of sigmoid in the right side of the pelvis may result in tenderness there. The sensitive transverse colon can generally be palpated in the midabdomen as it crosses the spine. The abdomen may be distended and tympanitic with excessive rumbling and gurgling noted on auscultation.

**Character of the Stools**—The third important feature of the syndrome is the objective evidence of bowel dysfunction afforded by the description of the stools. The patient's statement that he is constipated is significant but not trustworthy, for upon questioning one may find it to mean merely that the patient *thinks* he requires cathartics or enemas in order to avoid becoming constipated. Rarely do such patients leave their bowels alone long enough to ascertain whether they would function normally or not. However, many patients who are not cathartic or enema addicts nevertheless have hyperirritable digestive tracts. Some consider themselves constipated, others recognize the presence of a tendency to diarrhea. The significant feature in all is the fact that bowel function is altered to some extent, it is rarely normal.

For practical purposes, the normal defecation is considered as a well formed collection of feces an inch or so in diameter, several inches in length, and firm in consistency. True constipation exists when the fecal material is retained in the colon so long that excessive water absorption occurs with the result that the feces are passed as hard dry balls. This may result from atony or insufficient muscular activity, but much more frequently it is produced by excessive spasm. The presence or absence of pain gives an important clue in this differentiation, for pain usually means spasm. Equally significant is the passage of formed fecal material of small diameter, a caliber of an eighth to a quarter or perhaps half an inch, simulating the so-called lead pencil or ribbon-like formation of lead poisoning. Frequently the narrow caliber is erroneously attributed to a neoplasm of the sigmoid or to spasm of the anal sphincter, it is almost pathognomonic of spasm of the sigmoid.

Soft unformed or watery dejecta are indicative of hypermotility of the bowel, the material traversing the colon too rapidly to permit the proper absorption of water. Mucus is secreted throughout the digestive tract in response to irritation—the greater the irritation the more mucus. In some individuals so-called "mucous casts of the bowel" may be expelled. These consist merely of long shreds of dried and tenacious mucus. In some patients the intestinal hyperactivity is mani-

festated also by an excessive passage of flatus. The odor and color of the feces are not of diagnostic significance.

**Superimposition of a Functional Disturbance Upon an Organic Disease**—The diagnosis of a functional disturbance of the digestive tract is thus based upon such a syndrome and the reasonable exclusion of organic diseases, although the syndrome may be superimposed upon organic lesions. Thus the so-called *gallbladder dyspepsia* is in large measure at least such a functional disturbance occurring in an individual found to have gallstones. Cholecystectomy, characteristically relieves biliary colic,<sup>7</sup> the dyspepsia usually persists. In some instances the digestive symptoms may disappear following operation regardless of the procedure, be it cholecystectomy, gastro-enterostomy or something else. Conversely the so-called gallbladder dyspepsia may be relieved by the measures usually employed in treating a functional disorder and disregarding the gallstones, such a program, however, does not influence the biliary colic. In the so-called chronic non-calculous cholecystitis the symptoms seem attributable not to the gallbladder, but to the intestine, for they tend to persist after cholecystectomy and on the other hand may be relieved medically without cholecystectomy.<sup>8</sup> This fact seems to negate rather than support the concept that the symptoms in such cases are due to functional disorders of the gallbladder and biliary tract with spasm of the sphincter of Oddi. Fat intolerance is not a problem, for as a matter of fact it is not as characteristic of or as peculiar to gallbladder disease as it is generally considered.

This criticism of the concept of gallbladder dyspepsia applies equally well to *appendiceal dyspepsia* and so-called chronic appendicitis. Acute appendicitis and appendiceal colic are of course appendiceal in origin and call for appendectomy. So-called "appendiceal dyspepsia" or "chronic appendicitis" may also be relieved by appendectomy or by any other procedure, more frequently it persists and may be relieved medically by management as a functional disturbance of the bowel.

The more acute attacks of intestinal colic resulting from dietary indiscretions in individuals with hyperirritable digestive tracts simulate and indeed often cannot be differentiated from *staphylococcal food poisonings* or mild *salmonella infections*, although in the usual case the presence of fever, the suddenness of the onset and the severity of the illness serve to identify the attack. Occasionally one sees nausea, vomiting, abdominal pain and distention suggestive of paralytic ileus but subsiding rapidly as the irritability of the gut decreases.

#### ETIOLOGY

The etiologic bases for hyperirritability of the digestive tract are of two general types, the physiologic and the emotional or psychologic.

In the *physiologic* group the cathartic and enema habitués are conspicuous. Of course, it can be argued by those psychiatrically inclined that in these individuals the problem is not purely physiologic, for is not the habituation psychologically determined? Thus may be the case. It is also to be noted that many people use cathartics regularly for years without developing abdominal distress. Nevertheless, waiving for the moment the psychologic aspects of the problem, it is a fact that cathartic habitués with chronic abdominal discomfort and pain may be relieved of distress by teaching them to discard the habit and to regulate the bowels with diet alone.

Another large group of so-called dyspeptics are those who regularly indulge in dietary indiscretions or whose food habits lead them to consume a more laxative diet than they are able to tolerate. The irritating action of certain foods such as molasses, beer and cider are well known. All foods are more or less laxative, none are actively constipating. Some individuals habitually consume excessive amounts of irritating foods. Coffee is an intestinal stimulant and when used to excess may produce both distress and small calibered spastic bowel movements. Nicotine is likewise a stimulant of intestinal activity and seems to be responsible for many cases of "chronic indigestion."<sup>9</sup> Alcohol is also rather irritating. Schindler and Gray<sup>10</sup> and Berry<sup>11</sup> were not able to ascribe the morning nausea of the chronic alcoholic to gastritis, perhaps it is attributable to intestinal irritation.

Specific food idiosyncrasies and allergies doubtless exist in certain individuals, particularly for shell fish, raw eggs, and strawberries. Usually these allergic states produce in addition to the digestive disturbances urticaria or other reactions affording evidence of their true nature. It is of course possible that chronic allergic digestive disturbances may exist without such manifestations, but in most patients the mechanism seems more probably to be that of simple irritation. The results of so-called elimination diets must be appraised cautiously.<sup>12</sup>

The *nervous* or *emotional* component in digestive tract hyperirritability is most important and yet naturally enough difficult to measure.<sup>13</sup> Certainly there are countless instances in which the disorder is entirely psychogenic.<sup>14 15 16</sup> The physiologist may object at this point and say that while the phenomenon is psychologically determined the mechanism is physiologic, and so it is. Nausea, vomiting, abdominal distress, constipation and diarrhea may be phenomena as simple, as physiologic and as psychologic as blushing of the face. The well known diarrhea of fear is an example. Usually, however, the clinical picture is much more complicated, it encompasses the numerous chronic anxieties and frustrations of life with all its difficult and irreversible personal relationships. The physician usually wisely deals with his patient on the level of the conscious only and leaves to the psychiatrist those patients in whom exploration of the vast realm of the subconscious is necessary.



The problem of etiology may be summarized by the statement that in the great majority of patients afflicted with functional disturbances of the digestive tract there is a hyperirritable nervous system, psychogenically or emotionally determined or perhaps constitutionally hyperactive and inadequate to withstand stress combined with habits deleterious to the individual such as the constant use of cathartics, enemas, tobacco, alcohol, overeating or other dietary practices not well tolerated by the patient.<sup>20</sup>

### TREATMENT

The therapy of functional disorders of the digestive tract may be divided into those procedures based on physiologic desiderata and those based on psychiatric or psychologic considerations. The former are rather easily defined and outlined, for they deal with diet, medication, enemas and such objective procedures, the latter are intangible and difficult to define in nonpsychiatric terms for they depend too often on the "art" of medicine, upon more or less unconscious psychotherapy upon the attitude of the physician.<sup>21</sup> Arthur Hertzler<sup>22</sup> one of the ablest general practitioners of the old school and a shrewd judge of human nature, wrote at length on this subject, drew many amusing caricatures, and concluded with the following direct advice: "It is misleading to speak of stomach complaints as gastric neuroses. This designation suggests that the stomach is at fault but the stomach is not at fault. It is the patient who is nervous. Forget the stomach and cause the patient to forget it." There can be little doubt that in Hertzler's heart and practice there was an abundant warmth of understanding even though he may have had little knowledge of formal psychiatry and no comprehension of modern psychoanalytic concepts. The general practitioner of today is better prepared to cope with these phases of medicine, the practitioner of tomorrow will have a great advantage over his predecessors as a result of the general increase in psychiatric teaching and training now taking place in our medical schools and the numerous excellent books on the subject.<sup>18-20</sup> The social worker is often of very real help in acquainting the physician with relevant information and in assisting the patient to gain a better understanding and in numerous ways resolving trying situations.<sup>20</sup>

**Diet**—All food and drink is more or less stimulating or irritating to the digestive tract. Hence in acute disturbances a period of starvation is highly desirable its length depending upon the severity and duration of symptoms. The first substances to be given should be hot water, broth, barley gruel and weak tea followed by oven-toasted bread, cream of wheat, boiled milk, cooked eggs, rice, custard, jello and blanc mange (see section I of diet). As improvement occurs the diet may be increased and liberalized in accordance with the principles to be described.

In chronic disturbances the initial period of starvation is usually unnecessary and the limitation in food need not be nearly so strict. As a rule it is wise to give the patient a diet with certain specific instructions, although in some instances even this may be unnecessary

## DIET

### I FOODS WITH LITTLE IRRITANT AND HENCE BEST TOLERATED IN ACUTE DISTURBANCES

Water, weak tea, rice or barley gruel, meat broth, cream of wheat, oven-toasted bread, zwieback or toasted soda crackers with butter, soft cooked eggs, boiled milk, custard, plain jello

### II MORE SUBSTANTIAL BUT RELATIVELY BLAND AND EASILY DIGESTIBLE FOODS

Cereals with milk or cream	Macaroni
Refined rice	Noodles
Rice Krispies	Spaghetti
Rice Flakes	Vermicelli
Puffed Rice	
Cornflakes	
Puffed Wheat	
Oatmeal (well cooked)	

Soups	Consomme	Strained cream of potato soup
	Strained chicken broth	Strained cream of celery soup
	Strained vegetable soup	Strained cream of mushroom soup
	Strained cream of rice soup	Strained vegetable soup

Cheese	Cream cheese	Cottage cheese
	American cheese	Edam cheese
	Swiss cheese	

Fish	Salmon	Fowl	Chicken	Meats	broiled, boiled or roasted (or baked)
	Tuna		Turkey	Beef	Ham
	Whitefish		Squab	Veal	Liver
				Lamb	

Potato baked, mashed, or au gratin

Breads	White bread	Milk toast
	Toast	Hot biscuits of white flour
	Croutons	Hot rolls
	Bread sticks	Whole wheat bread

Milk products Milk, cream, cocoa, eggnog, butter

Other beverages tea, Sanka, Postum, coffee

Desserts	Vanilla custard	Bread pudding	Bavarian cream
	Caramel custard	Tapioca pudding	Snow pudding
	Floating island	Cornstarch pudding	Plain jello
	Rice custard	Spanish cream	Cottage pudding
	Angel food cake	Plain cake	Peter Pan cookies
	Cream puffs	Lady fingers	Hydrox cookies
	Eclairs	Sponge cake	Arrowroot cookies
	Icebox cake	Boston cream pie	
	Ice cream, plain	Pies	Custard
		Lemon cream	Chocolate
		Banana cream	
		Coconut cream	

## III. COOKED VEGETABLES, MORE LAXATIVE CHIEFLY BECAUSE OF GREATER RESIDUE

## A. Moderately irritating

Asparagus	Spinach	Tomatoes
String beans	Sweet potato	Beets
Carrots	Peas	

## B. More irritating

Artichokes	Rutabaga	Broccoli
Parsnips	Eggplant	Navy beans
Onions	Green peppers	Lima beans
Cabbage	Turnips	Squash
Cauliflower	Kohlrabi	Corn

## IV. COOKED FRUIT, MORE LAXATIVE BECAUSE OF CHEMICAL IRRITANTS

Prunes	Pears	Grapes
Peaches	Baked apple	Pineapple
Applesauce	Plums	Rhubarb
Figs	Cherries	Fruit pies
Apricots	Berries of all kinds	

## V. RAW VEGETABLES, MORE LAXATIVE

Lettuce	Endive	Onions
Celery	Tomatoes	Cabbage
Watercress	Radishes	Cucumbers

## VI. RAW FRUITS, MORE LAXATIVE

Banana (least laxative)	Pears
Oranges (juice, sections, whole)	Peaches
Grapefruit (juice, sections, whole)	Cherries
Apples	Grapes
Melon	Plums
Pineapple	Apricot
Berries of all kinds	Avocado Pear

## VII. MISCELLANEOUS FOODS, SOME VERY LAXATIVE, SUCH AS HONEY AND BEER

Ice cream with fruit	Pickles, olives, relishes
Ice cream with nuts	Catsup
Jam, jelly, marmalade, honey	Soft drinks Coca Cola,
Syrup	gingerale, sodas, cider
Nuts	Alcoholic beverages beer
Pop corn	wine, whiskey, etc.
Candy	Buttermilk

In practice, a diet form such as the one outlined may be used. This is, as given, a full diet arranged in a manner to enable the physician to delete rather easily certain articles of food or groups of articles. Many of the more irritating foods such as the raw fruits, vegetables and miscellaneous items listed in sections V, VI and VII may be prohibited entirely. A fairly satisfactory procedure is that of permitting the patient to eat all of the items in sections I to IV inclusive except for the more irritating cooked fruits and vegetables. The amount of cooked vegetable and fruit should be stipulated as perhaps two dishes of cooked vegetable and two dishes of cooked fruit. If the distress and

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Puffed Rice	
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	Strained chicken broth	Strained cream of celery soup
	Strained vegetable soup	Strained cream of mushroom soup
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	American cheese	Edam cheese
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	Tuna		Turkey	Beef	Ham
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Potato baked, mashed, or au gratin

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	Croutons	Hot rolls
	Bread sticks	Whole wheat bread

Milk products Milk, cream, cocoa, eggnog, butter

Other beverages tea, Sanka, Postum, coffee

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intestinal hyperactivity persist, these may be reduced or eliminated, if the symptoms disappear, qualitative and quantitative additions may be made to the diet. If the stools become hard and dry the amount of laxative food eaten should be increased, spinach, lettuce, whole wheat bread, prunes and figs being especially helpful.

**Rest and Exercise**—In patients with a very irritable colon, rest is of great value and conversely, in patients with atonic constipation exercise is helpful. The amount of rest indicated depends upon the severity of the disturbance. When the pain is severe, complete bed rest is in order. In the average case long hours of sleep at night and perhaps a nap or rest period in the afternoon are adequate. The amount of rest as well as the amount and type of exercise to prescribe cannot be stated categorically. Both are important. The exercise should not be too strenuous and it should give pleasure. The mechanism of the health-giving effect of physical exertion and of sunlight is not well understood but it is nevertheless definite.

**Antispasmodics and Sedatives**—Belladonna, a time honored and valuable antispasmodic, may be given in the form of the extract,  $\frac{1}{2}$  grain, or the tincture, ten to fifteen minims, three or four times daily. Phenobarbital is very helpful as a sedative and as an antispasmodic for it does inhibit intestinal activity. It may be administered as the elixir three or four times daily but preferably in tablet form,  $\frac{1}{4}$  to  $\frac{1}{2}$  grain three or four times daily. When insomnia exists, the phenobarbital may be used advantageously in a single dose of  $1\frac{1}{2}$  grains at bedtime. Other preparations such as seconal or nembutol may be substituted if preferred or if objectionable side effects appear such as dizziness. Occasionally, for short periods, the bromides may provide more satisfactory relaxation. Numerous other sedative and antispasmodic drugs are on the market but they have not proved superior to the older and cheaper drugs mentioned. The opiates increase the muscular tonus and are not desirable.

In most instances the application of external heat in the form of an electric pad or a hot water bottle affords symptomatic relief of the distress and seems to quiet the bowel. It may be used continuously, on alternate hours, or for an hour or two after each meal, depending on the severity of the discomfort. Burns must be carefully avoided. Hot stupes are commonly employed but are usually unnecessary. A hot tub bath often accomplishes surprising relaxation.

**Avoidance of Laxatives and Enemas**—Laxative preparations of all kinds including mineral oil are to be avoided. They irritate the bowel, teach the patient bad habits, and are unnecessary. This is true on the whole of the relatively mild so-called bulk-producing substances, although in general these are much less irritating than the laxatives. The frequent use of large enemas of various kinds is also to be decried.

One may use small water enemas of  $\frac{1}{2}$  to 1 pint to stimulate the defecation reflex in instances in which it is lacking and in which the stool tends to collect in hard masses in the rectum. The patient may need assistance in expelling such fecal impactions. At times it is necessary to break them up with the gloved finger and stimulate evacuation by means of a water enema. In such individuals the use of a retention enema consisting of three or four ounces of mineral oil or olive oil given at bedtime is helpful in softening the feces and restoring the defecatory reflex. Glycerine or soap suppositories are very effective in some patients afflicted with this condition. It is important to remember that fecal impactions usually form in the rectum not above it and that one need not worry if a few days pass without a bowel movement provided there is no accumulation of feces in the rectum. Constipation does not consist in the absence of a bowel movement for two or three or more days but in the passage of hard dry stools.

The interdiction against laxatives and enemas should not be carried to the point of prohibiting them under all conditions. There is no disease in which they are curative but they are of value in certain ways, as in the preparation of the patient for operation or for x-ray examination of the colon. Furthermore, many people for one reason or another develop the cathartic habit, experience no abdominal distress or ill effect therefrom, and should be allowed the privilege of continuing the habit even though it is unnecessary. Certain bedridden patients, if they obtain with a laxative a large daily bowel movement are happier than they are if they do not. This may be a fixation or 'preoccupation' on the part of the patient but in the absence of abdominal distress there is no objection to the habit.

**Résumé**—In the vast majority of patients with functional disorders of the digestive tract the physiologic program outlined above, together with the superficial psychotherapy involved in the exclusion of organic disease, the prescription of a diet together with medication and the reassurance thus given is sufficient to relieve the symptoms and restore normal gastro intestinal function. The physician should be continually on the alert, however, to detect undiagnosed organic disease and the many psychiatric disorders masquerading as functional digestive disturbances. These disorders are of all types: simple psychoneuroses in which an adequate adjustment is easily restored; complicated psychoneuroses seeming almost impossible to improve; mild or severe reactive and endogenous depressions; hysterics; migraines; schizophrenias; paranoias and all manner of combinations. For such individuals an experienced psychiatrist may prove to be of as much help in time of trouble as a surgeon is in the presence of an acute surgical emergency. However, both the surgeon and the psychiatrist should be consulted if possible, before the emergency arises.

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## RENAL INSUFFICIENCY REVERSIBLE AND IRREVERSIBLE

ROBERT F. LOEB, MD, F.A.C.P.\*

A HOPELESS prognosis is generally meted out to the uremic patient because decompensated renal insufficiency characterized by progressive nitrogen retention, appears as the terminal event in three common types of kidney disorders for which there are today no known cures. These disorders are chronic glomerulonephritis, arteriolar nephrosclerosis, and chronic pyelonephritis. On the other hand, decompensated renal insufficiency may be wholly reversible. It is the purpose of this clinic to emphasize this fact and to point out that the uremic patient is always deserving of study with whatever techniques may be essential in an attempt to determine the underlying cause of his renal failure.

Once the diagnosis of renal insufficiency with nitrogen retention is established, consideration should next be given to the all-important question of whether or not the underlying cause may be alleviated. In the accompanying table is given a partial list of disorders which may lead to decompensated renal insufficiency. It is apparent that the group of disorders in which renal failure may be present is extraordinarily diverse. It embraces disturbances which may be acute or chronic. It includes pathological states in which renal failure finds its origin primarily in a decrease in renal blood flow and not in significant primary parenchymatous disease of the kidneys. It includes disease in which renal failure is at times spontaneously reversible as well as those disorders which, despite all therapy, progress to a fatal outcome. It also includes a most important group of abnormalities in which there is mechanical obstruction to urine flow.

The cause of renal insufficiency is often apparent as, for example, in patients with well documented chronic glomerulonephritis. It is equally apparent in acute nephritis with generalized edema or in various types of poisoning. There is also little question concerning the mechanisms involved in patients in whom renal insufficiency is based upon an acute decrease in kidney blood flow. However in many patients, the reason for renal insufficiency cannot be clarified on the basis of the clinical history, physical examination, or the examination of the urine alone. In these patients the possibility that uremic manifestations may arise from partial obstruction to urine flow must be borne in mind. When the

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From the Department of Medicine, College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York City.

\*Lambert Professor of Medicine, College of Physicians and Surgeons, Columbia University. Associate Attending Physician, Presbyterian Hospital and Neurological Institute.

## DISORDERS THAT MAY LEAD TO DECOMPENSATED RENAL INSUFFICIENCY

## A Reversible Decompensated Renal Insufficiency\*

## I Due primarily to changes occurring in renal parenchyma

- (1) Acute glomerulonephritis
- (2) Carbon tetrachloride poisoning
- (3) Mercury poisoning
- (4) Sulfonamide nephrosis
- (5) Transfusion "nephritis"
- (6) Toxemia of pregnancy
- (7) Severe burns

## II Due primarily to decrease in renal blood flow

- (1) Severe dehydration and loss of inorganic base
  - (a) Diabetic acidosis
  - (b) Severe diarrhea
  - (c) High intestinal obstruction with excessive vomiting or enterostomies
  - (d) Adrenal insufficiency
- (2) Surgical shock
- (3) Cardiac insufficiency

## III Due primarily to obstruction to urine flow

- (1) Lesions of renal pelvis and ureteropelvic junction
  - (a) Urinary calculi
  - (b) Aberrant renal vessels
  - (c) Inflammatory disease with stricture formation
  - (d) Sulfonamide crystal deposits
- (2) Ureteral obstruction
  - (a) Bilateral stone
  - (b) Inflammatory disease of ureters with or without scar formation
  - (c) Sulfonamide crystals
  - (d) Pelvic tumor with compression or invasion of ureters
- (3) Obstruction near bladder outlet
  - (a) Prostatic hypertrophy or neoplasm
  - (b) Posterior urethral valve

## B Irreversible Decompensated Renal Insufficiency

## I Due primarily to changes occurring in renal parenchyma †

- (1) Chronic glomerulonephritis
- (2) Hypertensive vascular disease with nephrosclerosis
- (3) Chronic pyelonephritis
- (4) Polycystic disease
- (5) Amyloid disease
- (6) Bilateral renal tuberculosis

\* While the outcome in this group is often favorable, it is frequently dependent upon the type of therapy employed and the time at which it is instituted

† Although renal failure in this group is essentially irreversible, patients may continue an active existence over periods of many years despite the presence of nitrogen retention (renal decompensation)

cause of renal insufficiency is not certain beyond reasonable doubt, the patient should be subjected to a series of urological studies which serve to determine whether or not some form of obstruction is present and whether or not it can be relieved. These studies should be undertaken despite the presence of advanced uremia, because it is in this group of patients that remarkable restoration of renal function may result from the relief of obstruction, even when the prognosis would appear to be hopeless. Failure to employ all the necessary diagnostic procedures will needlessly sacrifice patients. The following case history serves as an example.

A thirty-one year-old woman with advanced rheumatoid arthritis entered the hospital in diabetic acidosis. She had not previously had symptoms referable to her urinary tract. Physical examination was essentially negative except for advanced arthritic changes and for her spleen, which was thought to be palpable. In the course of treatment of her diabetic acidosis, she received between 4000 and 5000 cc of fluid daily for several days. Her diabetes was easily controlled but her urine output was small and the specific gravity was low. Albumin was absent or at times present only in faintest traces. The blood nonprotein nitrogen level on admission was 43 mg per 100 cc.

After five days the patient developed pain in her left upper quadrant. The mass previously thought to be her spleen became very tender and was then thought to be a hydronephrotic kidney. The urinary output continued to fall and after three weeks a slightly tender mass appeared in the right flank. It was at this time felt that the patient had developed bilateral hydronephrosis for some reason in response to the large amount of fluid administered in the course of treatment of her diabetic acidosis. Cystoscopic examination was impossible because of ankylosis of both hips. The patient became anuric and passed only 140 cc. of urine in the last eighteen days of life. At the time of death her blood nonprotein nitrogen was 227 mg per 100 cc. At autopsy a fairly recent bilateral hydronephrosis was found and resulted from compression of both ureters by aberrant renal vessels.

The life of this patient might have been saved by the relief of mechanical obstruction had the possible cause of her renal insufficiency been considered and had both kidneys been explored surgically despite the fact that retrograde pyelography was impossible because of ankylosed hip joints.

#### DIAGNOSTIC PROCEDURES

It is obviously not practical to attempt to indicate specifically the diagnostic procedures which should be employed in any given case of renal insufficiency. Of first and foremost importance naturally is a well documented *history*, complete in all details relevant to blood pressure measurements, urinary symptoms and examination of the urine in years gone by. A few generalizations may help to clarify the usefulness as well as the limitations of the various methods of study employed.

1 *Retinal Changes*—In the presence of marked arteriolar narrowing, retinal hemorrhages, exudates and papilledema uremia is usually a

ciated with irreversible renal insufficiency. In rare instances, however, this combination of disturbances may be associated with acute glomerulonephritis which may terminate favorably. On the other hand, advanced renal insufficiency may be present without demonstrable changes in the eyegrounds. This is rarely the case in glomerulonephritis, nephrosclerosis and chronic pyelonephritis, but is more frequently true in forms of renal decompensation due to congenital anomalies and obstruction to urine flow which may be relieved by surgical technics.

2 *Blood Pressure*—Advanced renal failure may be present with or without arterial hypertension. Extreme degrees of arterial hypertension tend, however, to be associated most frequently with renal insufficiency which results from incurable disease of the kidneys.

3 *Urine Examination*—It must be emphasized that the degree of *albuminuria* in no way parallels the degree or severity of renal insufficiency. In patients with mechanical obstructions to urine flow, with advanced renal decompensation, albuminuria is often absent or minimal. The *low fixation of specific gravity* is unquestionably one of the most significant characteristics of advanced renal failure. Its presence does not, however, imply that renal insufficiency is irreversible. The relief of prostatic obstruction, for example, may be followed in time by a return of the power of concentration. *Pyuria*, when found in a "clean" specimen in the presence of renal insufficiency, should be considered as adequate grounds for cystoscopy and pyelography. The presence or absence of *urinary casts* is of little importance in determining the etiology of decompensated renal insufficiency.

4 *Nitrogen Retention*—The degree of nitrogen retention is not a measure of the reversibility of renal failure. It merely serves to indicate the presence of decompensated insufficiency. Determinations repeated from time to time indicate the trend toward or away from compensation.

5 *X-ray of Kidneys*—This finds its greatest usefulness in determining the possible presence of stone or of bilateral calcification in tuberculosis. Flat plates of the urinary tract also yield useful information concerning kidney size. Enlargement is easily recognized. On the other hand, if embedded in large fat pads, contracted kidneys may cast shadows of approximately normal size. This simple x-ray procedure should be carried out in all patients with progressive renal insufficiency.

6 *Catheterization of the Urinary Bladder*—This should be done to determine the volume of residual urine in all patients in whom the basis of renal insufficiency is not wholly apparent. It is of particular importance in males in whom prostatic obstruction may be present and in children with renal insufficiency without the degree of albuminuria usually present in glomerulonephritis.

7 *Cystoscopy and Retrograde Pyelography*—The importance of these procedures in the diagnosis of renal insufficiency of obscure ori-

gin cannot be overemphasized. All patients, both children and adults, in whom the cause of renal insufficiency is not apparent, should be cystoscoped. Pyelograms should be made to determine the patency and course of the ureters, to determine the presence of hydronephrosis or non-opaque stone, to determine the relative function of both kidneys and to determine the presence and type of infection. Pyelography is also of value to determine the presence of bilateral polycystic disease as a cause of renal failure.

8 *Intravenous Pyelography*—This procedure has relatively little value in the study of decompensated renal insufficiency because of the slow rate of elimination of the dye by renal tissue with diminished function.

9 *Surgical Exploration*—In rare instances as in the case of the patient described above, exploration of both kidneys is justifiable and indicated. Exploration with decapsulation of the kidneys may possibly be justifiable in acute renal decompensation resulting from sulfonamide nephrosis and other acute anuric states associated with marked edema of renal tissue.

# THE MANAGEMENT OF CHRONIC DISEASE OF THE NERVOUS SYSTEM

DONALD J SIMONS, M D \*

AND

HAROLD G WOLFF, M D., F A C P †

## THE MENTAL HYGIENE OF CHRONIC DISEASE

WHEN an individual is frustrated by difficulties in locomotion or in the use of his hands and yet possesses his usual intellectual faculties, the management of his attitudes is of the greatest importance. As this aspect of treatment is the least tangible and the most difficult, it is often neglected by the physician who too often considers it beyond his powers or too time-consuming. Such a physician may well ask himself if he can afford the time to practice medicine.

Physicians should beware of and watch for patients who, suddenly realizing that they are to be permanently disabled, sustain a total collapse of morale. They admit no interests, they demand help with everything, they indulge in self-pity. In these patients the problem is to prevent self-pity, to develop self-reliance, to reduce self-awareness, to avoid inertia, and to maintain interests outside himself.

**Prevention of Self-Pity**—These patients must be treated firmly from the inception. The physician should discuss the problems confronting the patient with the family and explain to them not only the nature and prognosis of the illness but also his plan of management. The family's help should be enlisted in controlling visitors and in advising them of the relevant parts of the situation. Some patients are quick to use physician, family and friends against one another.

The physician should also discuss the illness and the plan of management with the intelligent patient in such a way as to relieve anxiety and fear and to build up in the patient a feeling of security through confidence in his physician. During the first few weeks of illness sympathy is likely to be overdone. It is well to point out to the family that excessive sympathy engenders self-pity. Self-pity is one of the greatest evils afflicting the invalid. The physician must take pains to

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From the New York Hospital and the Departments of Medicine and Psychiatry, Cornell University Medical College, New York City

\* Assistant Professor of Clinical Medicine (Neurology), Cornell University Medical College, Physician to Out-patients, New York Hospital, Attending Neurologist, Midtown Hospital

† Associate Professor of Medicine (Neurology), Cornell University Medical College, Associate Attending Physician, New York Hospital, Assistant Attending Psychiatrist, Payne Whitney Psychiatric Clinic

avoid appearing unkind. He would do well to point out that he understands and shares the patient's feelings but that the frequent expression of that sympathy works against the patient's own best interests. An irritable, impatient physician may give his patients the impression that he thinks they are neurotic, malingering, or hysterical.

**Development of Self Reliance**—In a gentle but none-the-less certain manner it is necessary to make clear to every patient that he is expected to rely upon himself with respect to his physical comforts, his use of time, and the development of his interests and amusements. He must be "put on his own" and made responsible for his morale. The physician may point out to the patient that he should not lean too heavily upon sympathy or help.

It is often desirable to explain to the intelligent patient just what the limitations of his immediate situation are. (There is no need or excuse for detailing his ever-increasing future limitations.) One may point out that refusal to understand and accept the situation or that reactions of rage, futility and despair constitute emotional behavior designed to arouse sympathy. The patient must begin by trying to accept his handicaps with as little emotion as possible and by resolving to fend for himself to the limit of his ability.

An occasional patient will hesitate to accept his handicap thinking his disability temporary. Such a patient is avoiding the issue and has not understood his situation. He must be led to face reality and to deal with things as they are. When there is hesitation in undertaking self help, the physician must investigate its origin at once. What causes the delay—desire for sympathy? inertia? timidity? a lack of motive? shock at the realization of the handicap? a belief that his family does not appreciate his difficulty? a feeling that the objectives recommended are of little merit? At this point in the patient's relation to his illness, stagnation of his attitude may easily prove a handicap to any subsequent satisfactory adjustment. The patient must take some kind of action at once. He should be pressed to continue working at his job as long as he is employable. If unemployable, he must get out of the house daily by wheelchair if necessary, to maintain contact with friends and his former haunts. Bed rest must be avoided as long and as much as possible.

**Reduction of Self Awareness**—Patients with involuntary movements, abnormal postures, or masklike faces are acutely aware of their appearance. They often exaggerate in their minds the impression they think they make upon others, hence, an urge to withdraw from social contacts and to avoid friends is common. Exasperation over muscle weakness or involuntary movements causes patients to give up one activity after another before there is any need for it. In slowly advancing chronic disease the tendency to give up and withdraw may develop insidiously. Therefore, the physician must prevent any trend in this

direction A frank discussion of the desire to withdraw is sometimes indicated

**A Regular Routine**—Establishment of a regular routine is desirable. Fixed times for rising, for retiring, for baths, for meals, for reading, for the afternoon nap, for exercises, and for walks avoid the necessity of making decisions, diminish inertia, and serve to make the patient less aware of himself

**Cultivation of Interests Outside Self**—In contrast to the rather stern attitude toward the patient and his illness which has been detailed above, the physician may exert a more benign influence by calling attention to the fact that a vast amount of much-sought-after leisure time is now available for the many things which the patient has always wanted to do The patient should be induced to utilize this leisure to the fullest extent along constructive lines, for constructive efforts offer the greatest rewards in satisfaction

Museums may serve as a stimulus to drawing, painting, modeling in clay or plastercine, and to the study of the cultures of other peoples and of earlier civilizations Many museums have classes which are instructive and entertaining

Where the use of the hands is impaired, a course of reading may provide useful occupation Reading can be facilitated by placing a lap-board or card table across the arms of a chair to hold the book and by using a paper weight to hold the pages down

If vision is impaired, the patient may enjoy cultivating his musical tastes in a serious manner He may further profit by listening while someone reads aloud If this is not feasible, a Talking Book Machine may be purchased from the American Foundation for the Blind, 15 West 16th Street, New York City, for \$45 00 or rented from the U S Government through any local organization aiding the blind Recordings of books of all types are available throughout the country upon application to the New York Public Library, Fifth Avenue and 42nd Street, New York City

For those whose only handicap is blindness, schools are available to teach typing and the use of the dictaphone, also canning, weaving, and playing musical instruments Many other occupations, such as masseur or newsdealer, are open to the blind

When defects confine the patient to his bed or chair, jig-saw puzzles, chess, checkers, and card games such as Russian Bank or solitaire which do not require the player to hold cards in the hand are useful pastimes

The fact of making something and possibly of selling it is a powerful builder of morale Professional occupational therapists should be obtained to teach the patient how to work with leather or metal and how to weave, model with clay, or bind books according to the patient's capacity Creative activity diminishes the feeling of hopelessness which so often plagues the chronically ill.



## THE MANAGEMENT OF CHRONIC MOTOR AND SENSORY DISORDERS

**Myelitis (Myelopathy)**—Whether infectious, traumatic, or neoplastic, the general management of chronic myelopathy is the same. Since myelopathy is characterized by some degree of motor weakness (usually complete paralysis below the waist) and sensory impairment, almost all these patients are bedfast.

Where there is x-ray evidence of protrusion of bone fragments into the vertebral canal, operation is indicated. Intravenous hypertonic glucose and/or saturated solution of magnesium sulfate 100 cc by rectum should be given to reduce intrathecal pressure. Usually for three or four days after the injury the cord is markedly edematous, therefore, the dura should not be incised for the cord may rupture explosively.

In the case of myelopathy due to infection, the usual measures against the agent should be taken. Syphilis is a common cause of myelopathy.

For convenience in nursing, the bed may be turned so that the patient's head is at the foot end of the bed. Bed boards should be laid on the bed frame to support the mattress. A sponge rubber mattress or an air mattress should be placed upon the regular mattress and inspected twice daily to see that it maintains proper inflation. The mattress is covered with a blanket upon which the patient lies. No sheet is used. A blanket wrinkles less, is softer, and absorbs moisture better than a sheet. In the case of a fractured spine, a tightly rolled blanket secured by adhesive tape can be placed under the air mattress at the level of the fracture in order to secure the proper hyperextension. No pillow is used under the head. The position of the patient with respect to the blanket roll must be checked by the nurse every two hours, for the patient slides easily and imperceptibly on an air mattress.

In all cases the *care of the skin* is of the utmost importance. Bed sores can be prevented only by an exact routine. The patient should be turned every hour by the clock and with each turning the skin should be rubbed with alcohol and carefully and thoroughly dried. Sterile dusting powder should be applied between the toes and in any folds of skin. The patient should not lie on wrinkles in the blanket. Hyperemic areas should be painted with tincture of benzoin twice in every twenty-four hours. Munro<sup>5</sup> recommends that abscesses should be tapped and drained through a needle and syringe. Incision and drainage are contraindicated. Sloughs and gangrenous tissue should not be excised but should be allowed to drop off.

A small pillow should be placed under the knees to keep them bent. Another pillow at the baseboard of the bed may be used to keep the feet in dorsiflexion. The paralyzed extremities should receive passive and, if there is any motor power whatever, active exercise at regular intervals at least three times daily for ten to twenty minutes. The

serves to maintain muscle function and to prevent stiff, painful joints when anesthesia is not complete

Formerly, when there was loss of sphincter control, patients with myelopathy have died from ascending urinary tract infection. Urinary infection can nearly always be prevented by the use of tidal drainage and irrigation as described by Munro.<sup>6</sup> One of the sulfa drugs may be used to advantage if infection occurs. The patient should receive a daily soapsuds enema to prevent impaction or fecal incontinence. The occasional use of a rectal tube left in place may relieve gaseous distention of the bowel. Prostigmine methylsulfate 1 cc of 1:2000 solution may be given hypodermically every hour for three doses when abdominal distention is acute or obstinate. The blood pressure should be measured frequently during this treatment.

In the case of myelopathy following *fracture of the spine*, the patient may be gotten up in a wheelchair as soon as the fracture has healed. Functions lost through anatomic interruption of the fibers in the cord will never be regained. Functions lost through pathophysiologic interruption of nerve conduction may return gradually over a period of months. There is no way to determine which type of interruption has occurred in any given defect except by the observation of returning function.

**Syringomyelia**—Some patients with syringomyelia suffer from pain which may be due to the pressure of fluid within the syringomyelic cavity or the dragging of the fluid filled cord upon posterior roots. *Roentgen radiation* of the cord, 400 r units a week alternating from either side of the spine and covering a larger field than the clinical picture indicates, may help to relieve the pain. *Radium* has been used with beneficial results.

When there is evidence of a spinal fluid block and x-ray is not helpful in relieving pain, a surgical drainage of the syringomyelic cavity with rhizotomy of any distorted posterior roots is indicated. Some surgeons have advocated keeping the myelotomy incision open by inserting small slips of rubber down into the cord incision and clipping them in place with silver clips.

**Myasthenia Gravis**—Myasthenia gravis may be distinguished from the weakness of hyperthyroid disease by the fact that it does not respond to iodine but does respond to prostigmine. The absence of atrophy and the normal creatine metabolism separate it from muscle dystrophies. Morning fatigue and weakness—manifestations of psychoneurosis—do not affect specific muscles. Bulbar palsy gives a different history, shows atrophy of the tongue, and has a rapid downhill course.

The basis of the treatment of myasthenia gravis is *rest* and the *avoidance of physical and emotional strain*. Fatigue invariably provokes the symptoms and untoward emotion may precipitate severe muscle weakness.

Thymic tumor is found at autopsy in about 50 per cent of patients with myasthenia gravis. If suspected, operative exploration is indicated in patients who are average surgical risks.

Glycine 20 gm (4 teaspoonfuls) daily may be taken in ginger ale with benefit in mild forms of myasthenia. Ephedrine sulfate 25 mg ( $\frac{3}{8}$  grain) is more effective and may be used by itself or as a supplement to glycine.

The most potent *drug* is prostigmine bromide available in 15-mg ( $\frac{1}{4}$  grain) tablets and prostigmine methylsulfate available in 1-cc. ampules containing either a 1:2000 (0.5 mg) or 1:4000 (0.25 mg) aqueous solution for intramuscular use. Full function will not be restored by prostigmine and the dose should not be increased in the hope of completely restoring function.

Deep *x-ray radiation* of the thymus is recommended for patients who are not doing well or who are getting worse.

In young individuals whose symptoms are inoderately severe, excision of the normal thymus may be considered. In our experience operation has benefited about half of the patients who submitted to it. Since the operative risk is great, the question of operation should be fully explained to the patient and his family. The responsibility of accepting or rejecting operation should lodge with the patient or his responsible relatives.

**Headache**—Headache is probably the commonest complaint in medicine. Its causes are manifold but only the two commonest varieties can be discussed.

*Migraine headaches* are paroxysmal throbbing mild to severe aching pains usually unilateral at the onset, located in the forehead temple, behind the eye, or occasionally above the mastoid process, sometimes preceded by visual scotomas or scintillations and other sensory manifestations, and frequently accompanied by nausea and/or vomiting "sickness" and chills. Occasionally diarrhea excessive lacrimation or fever up to 39° C. (102° F) may occur. This condition commonly runs in families.

*Tension headaches* are steady, dull to severe aching pains in the frontal or occipital regions often described as pressure pains or a tight band around the head. They are commonly associated with tight cords in the neck and soreness in the distribution of the trapezius muscles. Though usually bilateral they may be unilateral and they may be associated with aching muscles in the jaws, shoulders, or arms.

The mechanism of the migraine headache is painful distention of branches of the cranial arteries and the mechanism of the tension headache is sustained contraction of the muscles of the neck and scalp.

Emotional states, such as frustration, resentment, hostility and humiliation associated with abrupt change in the pace of living such as occurs on holidays or week-ends together with physical fatigue act

vate the migraine mechanism. Hurry, worry, anxiety and work under pressure activate the muscle tension mechanism. Tension headaches often occur in association with migraine.

The fundamental treatment of these headaches is *not* the use of drugs. Vasoconstrictors, of which ergotamine tartrate, 0.5 mg intramuscularly, is the best, and analgesics (aspirin, codeine) may be used for the symptomatic treatment of a migraine attack. Massage, the application of moist heat, or the injection of not more than 20 cc. of 1 per cent procaine into the neck muscles will relieve tension headache. The injection of procaine should not be done repeatedly. Its greatest usefulness is in interrupting prolonged attacks of pain. Before injecting procaine, one should pull back on the plunger of the syringe to make sure that the needle is not in a vein.

The treatment of the *underlying causes* for these headaches centers about evaluation and demonstration to the patient of the characteristics of his personality, its aims and its frustrations, and in examining his physical and emotional environment with a view to a better regulation of himself, his desires, his attitudes, and his activities. The physician should in the course of this review of the patient try to enable the patient to become aware of his tension as it is developing or of the onset of fatigue and to accept these phenomena as warnings of pernicious behavior.<sup>9</sup> The special services of a psychiatrist will be needed for this task in some cases.

The daily or twice daily use of a "*relaxing bath*" is often helpful in obtaining muscle relaxation, rest, and the relief of feelings of pressure. Instruct the patient to fill a tub full of water the temperature of which when tested with the hand is neither hot nor cool (approximately 96° to 98° F). The eyes should be shaded from direct light. A folded towel or sponge should be used as a head or neck rest. The patient should be completely relaxed nearly flat on his back in the tub and covered as much as possible by the water for thirty minutes. This is followed by gentle drying.

**Convulsive Disorders**—The most important feature in the management of convulsive disorders is the determination of the cause. A seizure should be looked upon as a symptom until proved otherwise. In the newborn, congenital anomalies and birth injuries are common causes of fits. In infants with a convulsive diathesis, an acute infection may begin with seizures. Convulsive attacks occurring for the first time in an adult may be caused by syphilis, brain tumor, poisoning, or vascular disease. Consultation with a neurologist who can make a detailed study of the nervous system and who has facilities for electroencephalography and possibly pneumoencephalography is essential.

If no cause for seizures can be found upon detailed study and continuous observation, then the attacks may be considered cryptogenic convulsions of the grand mal, petit mal, automatic, or combined types.

In the treatment of fits, first place should be given to the *psychological aspects* of the problem. A basis for the management of such disorders should be laid with a review of the patient's personal history and an understanding of the social and personal problems which confront him. It is well established that emotional upsets may precipitate attacks in persons subject to seizures. Much can be done for the patient by the physician's taking interest in the patient's emotions and conflicts and by adjusting his life situation.

No patient who has fits should be permitted to drive an automobile or any other motor-driven vehicle. Bicycle riding in city traffic should also be forbidden. In the company of a responsible person swimming is permissible.

*Diet* may be unrestricted except in the matter of fluids. Patients whose attacks are not readily controlled by medication should restrict the total fluid intake including soup to not more than four glasses in twenty-four hours in winter or six glasses in summer. The ketogenic diet is both unpalatable and difficult to prepare, its usefulness is therefore limited.

Among the useful anticonvulsant *drugs* phenobarbital is the drug of choice. It is effective and toxic reactions (skin lesions) are extremely rare. For small children it may be given in the form of elixir of phenobarbital 1 teaspoonful (0.015 gm [ $\frac{1}{4}$  grain]) once to four times daily after meals as the frequency of the attacks warrants. Adults may be started with phenobarbital tablets each 0.03 gm ( $\frac{1}{2}$  grain) once to three times daily after meals according to the frequency and severity of the attacks. If this dosage is inadequate to suppress attacks, the intake may be increased up to 0.1 gm ( $1\frac{1}{2}$  grains) four times a day. If a patient fears the loss of his job should he have another attack, he may be started with this latter maximum dosage which can be later gradually reduced. In no case should the drug be suddenly omitted or drastically reduced in amount, for seizures may be precipitated by this means in persons who are taking the medication for other reasons and who have never before had a fit. Patients should be given a reserve prescription and warned about the hazards of running out of medicine.

Sodium bromide 1.0 gm (15 grains) in tablet or solution form may be used by itself or in addition to phenobarbital if either alone is inadequate. Because of the frequency of bromide rash this drug is unpopular.

Should both of these drugs prove inadequate, diphenylhydantoin sodium (Dilantin Parke Davis & Co) 0.1 gm ( $\frac{1}{2}$  grains) once to four times daily may be used together with phenobarbital for both together may be more effective than either one alone. This preparation is often quite effective but it is also dangerous. Untoward symptoms resulting from it are not infrequent. All patients taking this preparation should be examined and questioned at monthly intervals.

for poisoning may develop suddenly even after a year's successful use. Untoward effects are manifested by overgrowth of the gums with excessive bleeding, failing attention, memory and concentration, unsteady, staggering gait, awkwardness and tremor of the hands, and purpura. Intellectual deterioration may result if the drug is not withdrawn. Death has been reported as a result of purpura. Fortunately, the minor symptoms clear up readily upon withdrawal of the drug.

*Narcolepsy*, or uncontrollable sleepiness, may be treated by amphetamine sulfate (benzedrine) which is available in 5-mg ( $\frac{1}{12}$  grain) and 10-mg ( $\frac{1}{6}$  grain) tablets. It is seldom necessary to give more than 20 mg ( $\frac{1}{3}$  grain) in one dose. The frequency of administration will vary with the patient. Constipation, loss of appetite, and sweating are some of the unpleasant side reactions of this drug. Ephedrine sulfate 25 mg ( $\frac{3}{8}$  grain) has also been used with good results but it is less effective than amphetamine.

*Catatlexy*, or sudden muscle weakness associated with emotion, is not known to respond to any type of medication. The possibilities of psychotherapy have not been adequately explored.

*Herpes Zoster (Shingles)*—Although herpes is not a chronic disease in young persons, it may become a chronic painful state in older persons. Treatment should begin with the skin lesions.

*For the herpetic lesions*, zinc stearate powder and a bandage to prevent rubbing of the clothes over the hyperesthetic skin, or, if the lesions are painful, 1 per cent cocaine ointment with lanolin may be used. Collodion may be used to protect lesions on the face. Where lesions threaten the eyeball, the lid should be kept closed and the eye covered. The pupil should be kept dilated with sterile 1 per cent atropine sulfate solution, one or two drops daily. The possibility of glaucoma secondary to atropine must be considered and, should it develop, suitable treatment must be instigated.

*For the pain*, acetylsalicylic acid 0.3 to 0.6 gm (5 to 10 grains) may be used every two to three hours. In this condition there is danger of morphine addiction developing because of the prolonged period of pain, therefore, morphine should never be used. Pain is likely to be troublesome in direct proportion to the age of the patient. In the youthful it is seldom a problem, in the aged it may persist for months. In many cases the fear that the pain will never go is more troublesome than the actual pain. It is well to tell the patient at each visit that his pain *will* disappear in the course of time. The pain seldom lasts more than twelve to eighteen months in any event. X-ray therapy in small doses directed against the diseased dorsal spinal ganglia is said to be helpful in some cases.

For severe postherpetic pain, section of the posterior roots and chordotomy have been tried, but neither offers any certainty of relief, the latter is the more likely to prove helpful but its danger is great!

**Parkinsonism (Paralysis Agitans)**—In parkinsonism the attentive, never-despering attitude of the physician is especially of great importance. The remarks made in discussing the mental hygiene of chronic disease of the nervous system apply here particularly.

Passive manipulation of the extremities with stretching of the muscles morning and evening may relieve some pain, prevent contractures, and remind the patient that something is being done to help him. Patients confined to a bed and chair existence may appreciate the chance every hour or so to walk ten to twenty feet with the help of one or two persons. This is to be urged for its psychological more than for its physical value. When tremor affects the feet, calluses often form where the foot rubs the shoe, and other lesions may appear where one toe rubs against another. Lamb's wool, obtainable at most drug stores, keeps the skin dry and rubbing toes separated. It is superior to cotton wool. The periodic attention of a chiropodist may be desirable. Patients who spend most of the time sitting down should sit for at least twenty minutes three times daily with their feet elevated above their knees to avoid edema of the feet. Where skin lesions occur this is essential.

Once such a patient starts taking medicine it is difficult to wean him from it. Since the course of this illness may extend over many years, it is therefore wise, especially in patients under fifty years of age, to withhold drugs as long as possible. The young should use drugs only on special occasions and for special needs. Some patients may have considerable tremor and yet not be troubled by it; these should not take drugs. Others may have a moderate tremor which interferes with work or annoys when they are in company; these may take medicine as needed to meet a special occasion.

Those who have marked and troublesome *rigidity* will benefit by the following prescription:

R. Scopolamine hydrobromide tablets each 0.3 mg.

Label: One tablet three times daily.

Scopolamine hydrobromide is also available in 0.6 mg. tablets. Tremor is not influenced by drugs as much as is rigidity. It is often best to space the dosage by taking one tablet on rising, one on retiring to help in getting to sleep, and one midway between these times. Elderly patients frequently awake in the early hours of the morning and can not get to sleep again. A tablet and a glass of water placed by the bedside at retiring and taken upon early awakening usually permit sleeping three hours longer. A maximum dosage may be six 0.6 mg. tablets daily. Dark glasses may control any discomfort from pupillary dilation when outdoors in bright summer sun or sun on snow. Dryness of the mouth may be combated by chewing gum or by using lemon drop candy.

Another drug useful in treatment is prescribed as follows:

R̄ Tincture of stramonium

240 cc

Label Fifteen drops three times daily in water after meals

The dosage may be increased up to 60 drops three times daily. Since this preparation may lose potency on standing, patients should not use material which has been standing indefinitely in their medicine cabinets. It is sometimes desirable to give scopolamine for three months followed by tincture of stramonium for one month in alternation.

While both of these drugs may cause some dryness of the mouth, atropine is more effective where *drooling* is the major complaint. It may be given in tablet form, but the dose is more easily varied when the solution is prescribed.

R̄ Atropine sulfate (0.5 per cent solution)

30 cc

Label Three drops three times daily after meals. Increase dose by 1 drop every third day up to not more than 20 drops per dose, then gradually reduce dose until adequate maintenance dose is found.

Pain due to muscle rigidity can be diminished by quinine sulfate pills\* in doses up to 0.3 gm (5 grains) three times daily.

Some patients are able to manage *festination* by carrying a cane in front of them as impediment.

*Weakness* is the most troublesome of all complaints and the least amenable to treatment. Amphetamine sulfate (benzedrine) in 10-mg tablets on arising and again not later than 4 P.M. may be of some benefit.

Phenobarbital increases the weakness in advanced cases to a distressing degree and should be avoided.

Patients who are bothered by *weakness* or who are given to *depressed spirits* may be helped by 2.5 to 5 mg of dextro-amphetamine sulfate (Dexedrine sulfate, Smith, Kline & French) after breakfast.

The use of 30 to 45 cc of sherry or vermouth or 20 to 30 cc of whiskey served, according to the patient's taste, once or twice daily, is often of great service particularly in the most handicapped patients, for it dulls the patient's awareness of his difficulties. Since some persons react to alcohol with depression, irritability, or some other undesirable response, judgment should be exercised in prescribing alcohol.

**Tabes Dorsalis**—The manifold symptoms of tabes dorsalis are best managed by the "minimal prescribed routine therapy" described by the Cooperative Clinic Group.<sup>7</sup> This consists in twenty arsenical injections given in courses of six or eight injections in conjunction, either continuously or intermittently, with fifteen injections of bismuth or thirty injections of mercury succinimide. "If during the first year of treatment of tabes dorsalis, or after twenty injections of arsphenamine and heavy metal, the spinal fluid is still positive, supplemental treat-

\* Quinine is not obtainable for this purpose during the war.



ments should be employed." Supplemental treatments are a course of twelve to fourteen fever paroxysms, and/or not less than thirty injections of tryparsamide.

Physicians should take note of the fact that in a previously untreated case a few injections may activate the luetic process and interruption of treatment at this stage sometimes proves disastrous. Patients should be warned that once treatment is begun it must be continued for at least one year and preferably for two years.

During the course of this routine treatment, some symptoms may require special attention. Patients troubled by *ataxic gait* should practice Frenkel's walking exercises for at least fifteen minutes at regular periods every day. Three times daily is an absolute minimum. Hourly is not too often. Their purpose is to coordinate vision with foot movement. To practice these exercises the patient should learn to stand upright with support. This is the first step in the process of regaining confidence. Subsequently with the support of one or two persons he should learn to walk placing his feet on bits of paper which have been laid on the floor in a straight course in the footsteps of a person walking normally. Sometimes a rug design instead of papers can be utilized for this purpose. Finally, the patient should walk the mapped course unaided. A will to learn to walk and patient practice are necessary to obtain results. Unless absolutely necessary, a patient with *tubes dorsalis* should not be allowed to remain in bed except when sleeping because the proprioceptive functions of the spinal cord may deteriorate rapidly from disuse.

Attacks of *lightning pains* in the legs are best treated by aspirin, codeine and whiskey. Supervision of this treatment by the physician or by a responsible relative is advisable, for patients are often led to excessive dosage. Thiamine chloride in large doses intramuscularly has not been proved to be useful.

In severe attacks of *gastric crises* it is advisable to put the patient to sleep with an intramuscular injection of scopolamine hydrobromide 0.6 mg ( $\frac{1}{100}$  grain) and morphine sulfate 15 mg ( $\frac{1}{4}$  grain). When the patient is deeply asleep he should be given slowly a phlebotomy or hypodermoclysis of 1 liter of isotonic saline and 5 per cent glucose. This should be administered whether or not there has been vomiting because in any severe attack of pain the patient loses a great deal of fluid and chloride through perspiration and heavy breathing. Should the patient when awakening appear to be still in pain he should be induced to void. If the patient is unable to take medicine by mouth a solution of 0.16 to 0.6 gm ( $2\frac{1}{2}$  to 10 grains) of sodium phenobarbital in 10 cc of sterile distilled water intravenously at a rate not exceeding 1 cc per minute should be given until the patient is again asleep. To exceed this rate of injection is to court disaster in the form of cessation of respiration.

Frequently crises will terminate with a single narcosis. Occasionally severe attacks will last several days. In this event, the patient may be kept narcotized by repeated cautious injections of sodium phenobarbital. He should be allowed to awaken enough to void, but it is well to give nothing by mouth unless it be sodium phenobarbital. Fluids and chlorides must be maintained by clyses.<sup>8</sup> Since these patients readily become addicts, morphine should be avoided.

If crises are severe and frequent, a bilateral high cervical chordotomy must be undertaken by a competent neurosurgeon in spite of its risk.

*Optic atrophy* is one of the most difficult manifestations of tabes to treat successfully. It rarely responds to any form of chemotherapy.<sup>4</sup> When optic atrophy or visual field defects are found in their early stages, the patient should be given fever therapy at once. Malarial therapy—ten to twelve paroxysms—is preferable to artificial fever or typhoid inoculations. If fever therapy has been used and optic atrophy progresses, then a craniotomy for exploration of the optic chiasm is warranted. Frequently a thickened arachnoid membrane will be found compressing the chiasm. These membranes should be dissected and removed.<sup>2</sup>

For the atonic *tabetic bladder*, Langworthy<sup>3</sup> has found that acetyl- $\beta$ -methylcholine chloride (Mecholyl, Merck) 0.2 to 0.5 mg (3 to 7½ grains) is an effective drug in improving the contractile power of the bladder muscle and in decreasing the amount of residual urine "practically to zero." Thus drug is contraindicated in asthma, it should be given cautiously to elderly patients. Should residual urine become a problem beyond the power of mecholyl, the use of a sulfa drug and/or daily catheterization may become necessary to control cystitis. Since the loss of bladder sensation is the primary difficulty in the tabetic bladder, patients must be taught to void at regular intervals to prevent stretching of the bladder muscle. Splinting of the abdominal wall with the hand may prevent kinking of the urethra, and manual pressure against the bladder may aid in micturition.

**Multiple Sclerosis**—Some of the symptoms of multiple sclerosis can be helped by drugs. Urinary urgency and frequency may respond to ephedrine sulfate 0.025 to 0.2 gm ( $\frac{3}{8}$  to 3 grains). Spasticity is often benefited by quinine sulfate 0.3 gm (5 grains), three times a day. When the patient is depressed in spirits, dextro-amphetamine sulfate (Dexedrine sulfate, Smith, Kline & French) 2.5 to 5 mg after breakfast may greatly improve his sense of well-being.

Although multiple sclerosis may be due to some type of deficiency, at the present time there is no indication for specific vitamin therapy.

**Subacute Combined System Disease (Pernicious Anemia)**—In treating macrocytic hyperchromic anemia accompanied by disease of the nervous system, many physicians are satisfied to administer only sufficient amounts of liver extract to maintain the red blood cell count at five

million. This treatment may not be adequate to prevent degeneration of nerve tissue.

Presumptive evidence of the type of damage to the nervous system commonly found with macrocytic hyperchromic anemia is the complaint of numbness or prickling and tingling in the finger tips or toes. Less commonly, a stiff, awkward gait is noted. Examination of such patients may reveal diminished ability to perceive the vibrations of a tuning fork placed on the distal end of the radius or tibia. A patient may also be unable to tell whether he has been touched by one point or by two when the examiner touches the patient's unseen palm with divider points 2 cm apart. The perception of passive movement and of the direction of movement when the big toe or a finger is moved by an examiner may be diminished.

When these symptoms and signs begin or progress during treatment, it is evident that the patient is not receiving adequate amounts of the essential substance or substances. Treatment is best carried out by intramuscular injection of the less purified and less concentrated preparations of liver extract. The volume and frequency of injection will depend upon the results obtained, and may considerably exceed the average daily dose of liver of 1 USP unit intramuscularly. No disturbances follow excess in dosage. The adequacy of treatment can be determined only by repeated neurological examinations and the patient's freedom from complaints referable to disease of the nervous system.

**Nouritis (Neuropathy)**—Neuritis is commonly a prolonged and often a painful illness. Bed rest is essential. A search for the cause among toxic, traumatic and infectious agents, and nutritional deficiencies is indicated. Well-padded cock-up splints for the wrists and right angled splints or other devices for the feet are necessary to prevent contractures. The skin requires special attention as detailed in the discussion of Melopathy on page 437. A sponge rubber or an air mattress may be required if bed sores are imminent. When there is much pain, a cradle should be placed over the legs to support the weight of the bed clothes. In any case, the bedclothes should not be pulled tight over the feet.

Within the limits of tolerance, passive and active exercises and massage should be carried out regularly to keep the muscles and joints limber. Analgesics except morphine and sedatives may be used as needed. Except in nutritional deficiencies where treatment with all the vitamins is required, there is no experimental basis for administering vitamins in the treatment of neuropathy. During the painful stage of the disease dry heat in the form of infra red lamp warm packs or electric pads, is helpful. Great care must be used in applying any form of heat for where there is sensory loss, the tissue is easily burned.

Massage and active exercise, in a pool when available, should be used regularly after pain has subsided

**Cerebral Palsies of Children**—These conditions fall into two groups *cerebral diplegia*, which is a congenital developmental defect, and other motor defects resulting from *intracranial hemorrhage due to birth trauma*. The latter conditions are often manifested at birth by respiratory difficulties and later by unsatisfactory feeding. Subsequently, unilateral motor weakness, rigidity, or adventitious movements may be observed. In all infants who have a history of poor nursing followed by some form of motor defect, the spinal fluid should be examined for red cells, xanthochromia, and for its protein content. Pneumoencephalograms should also be made to determine the size, shape and position of the cerebral ventricles and the presence of normal cortical markings. By this means subdural hematoma or hydroma may be diagnosed.

In congenital cerebral diplegic patients, little can be done until the patient reaches an age where he can understand instructions and cooperate in training exercises. In children of low intelligence, the results of any type of training are likely to be so poor as to make training worthless. For spastic children able to cooperate, a graded program of active exercises training motor coordination should be instituted. Rhythmic passive exercises should be carried out by a therapist experienced in this type of work. Routine passive exercises alone are not satisfactory since they exercise all muscles without coincidental instruction of the patient in the voluntary relaxation of antagonist muscles. For older children and adults who are troubled with incoordination of movement, stringing large beads on heavy string and practice with a typewriter may help to train finger dexterity. Visual training aimed at focusing the gaze on his own thumb during hand movements or upon the lips of the person to whom he is speaking correlates visual and motor activity and reduces adventitious movement. The use of a microphone and loudspeaker is helpful in speech training.

The reduction of light stimuli by wearing dark glasses and of sound stimuli by using earplugs reduces the quantity and the intensity of involuntary movements. Eating may be facilitated by serving food in a circular dish with curled in edges.

For adults the use of a cocktail before dinner will materially aid in relaxing the muscles during eating. Some adults find a cocktail of great help in walking on icy sidewalks.

Since fear, anxiety and self-consciousness are important factors influencing spasticity, incoordination and athetosis, the training and control of emotional factors is important.

Children are helped by separation from normal children so that their handicap is less obvious to them. Education and treatment in classes with children who have similar handicaps are often of great psychological advantage.

These patients require the help of specially trained teachers and therapists. Enthusiastic or inspired teachers are of great therapeutic advantage.<sup>1</sup>

**Spasmodic Torticollis**—Spasmodic torticollis is a periodic, nearly constant, involuntary turning of the chin and tipping of the ear toward the shoulder. It is usually psychogenic in origin. It should be differentiated from similar conditions in which spasmodic slow contractions of muscles occur elsewhere in the body, for such patients are considered to have disease of the basal ganglia.

The primary concern in treating spasmodic torticollis is to discover and remedy the psychological causes leading to this abnormal reaction. Investigation may be carried out along the lines suggested in the treatment of Headaches (see page 440).

Symptomatic treatment consists in teaching the patient to recognize the feel of muscle contraction and to relax consciously the muscles involuntarily contracted. Quinine sulfate 0.13–0.3 gm (2 to 5 grains) may aid in relaxing. Heat applied to the neck muscles and deep massage may be of temporary benefit. Relaxing baths (see page 440) may also be of use in getting general muscle relaxation.

**Amyotrophic Lateral Sclerosis and Progressive Spinal Muscular Atrophy (Chronic Poliomyelitis)**—Both of these diseases are manifested by slowly progressive degenerative disease of the anterior horn cells of the spinal cord and characterized by weakness, atrophy and fasciculations. The former also shows evidence of widespread cortical ganglion cell degeneration and corticospinal tract disease characterized by increased tendon jerks and pathological plantar responses. The latter shows diminished or absent reflexes.

As no specific treatment is known for either of these diseases care of the patient must consist in detailed attention to his mental hygiene.

Excessive exertion and fatigue and exposure to inclement weather, the extremes of temperature, and to persons suffering from any type of infection of the respiratory tract should be avoided. Stimulants are well avoided, but 45 cc of sherry or vermouth or 20 to 30 cc. of whiskey twice daily for the patient whose disease is advanced may help to diminish painful awareness of the condition. The claims advanced for the beneficial results of alpha tocopherol and other forms of vitamin therapy have not been substantiated.

**Apoplexy**—The term "apoplexy" applies to cerebral hemorrhage, thrombosis and embolism. The treatment of the patient who survives the acute phase of a vascular accident is essentially the same regardless of the type of accident, for the disability results from the necrosis of brain tissue secondary to loss of the blood supply. Hemiplegia with or without language defect is the common result of apoplexy.

**Acute Period**—In the acute period the patient should be kept in bed. The bed must be kept free from crumbs and wrinkles, for these may

damage the skin. The bed must be kept dry. This can be facilitated in the case of the incontinent patient by laying newspaper interlaid with oakum or other absorbent material under the patient's hips. It is well to have the patient sit up in bed with the sound foot braced against a bed roll or some other soft but firm support in order to prevent the patient from sliding down in bed, thus hampering respiration. The paralyzed foot should be kept in a well-padded removable cock-up splint with the knee slightly flexed over a small pillow. A cradle should support the bedclothes over the foot. The shoulder girdle should not be elevated. The upper arm should be abducted about 75 degrees. The forearm, also supported by a padded cock-up splint, may be placed on a pillow with the wrist considerably higher than the elbow. The patient's position should be changed every two hours by lifting—not dragging or pushing—the patient. Sometimes the patient can shift himself by means of a rope suspended from a frame above the bed.

It will facilitate the use of a bedpan if the surface which comes in contact with the skin is well powdered. The bedpan is most easily utilized by rolling the patient onto his side, placing the bedpan in position, and then rolling the patient back onto it.

It is inadvisable to use strong cathartics or mineral oil, for hemiplegic patients often have poor sphincter control and they may suffer considerable humiliation from soiling themselves.

Fecal impactions may be managed by seating the patient upon a commode chair. The patient should bend forward acutely against a sturdy chair. A slow-flowing enema is then administered through a 2-inch nozzle. Manipulation of the nozzle is often sufficient to break up and dislodge the impaction. Occasionally manual extraction is necessary. A teaspoonful of lysol in the bottom of the commode pan will counteract offensive odors.

Light superficial massage and deep kneading massage are both indicated. Passive movements of the paralyzed joints must be executed whenever the patient is moved and at least every three hours during the day in order to prevent pain in the joints and muscles. Active movement, at first in a horizontal plane and later against gravity and increasing resistance, must be persistently urged from the start before spasticity appears. The patient should be given a rubber ball to squeeze and roll in his fingers. Few hemiplegic patients ever recover completely and the family may be so informed early in the illness, but recovery may be aided by persisting in muscle training.

*Subsequent Management*—After the acute period, the patient should be taken out of bed as soon as possible for periods of increasing length each day. Relatives and attendants should be instructed on how to help a hemiplegic patient out of a chair. Always pull on the hemiplegic side. Place the right foot against the patient's right foot, if that be the hemiplegic side, and rest the right knee against the patient's right knee. With

the right hand grasp the patient's right upper arm from the inside and the back and pull steadily

Walking should be encouraged either with a walking frame the support of two persons, crutches, a cane, or a brace to prevent toe drop

The physician should warn every attendant concerning the use of hot water bottles on the paralyzed and often hypesthetic side of the body Before applying any warming device to the skin of a patient, the attendant should first apply it to his own face for fifteen seconds to test its temperature

The treatment of *aphasia* requires much patience and devotion and is not always rewarding Treatment may be started by showing the patient a single object or picture of an object and simultaneously naming it verbally and graphically This is repeated indefinitely with the same and with different objects until new associations are made The process is much the same as in teaching a small child but progress may not be so rapid

**Hereditary Diseases**—There remains to be mentioned a group of rare diseases which are usually hereditary and familial in incidence They have nothing in common Friedrich's ataxia Marie's hereditary cerebellar ataxia, hepatolenticular degeneration (Wilson's disease) Huntington's chorea, the myelopathies, and amyotrophies make up most of this group

Since no treatment of any value is known for any of these diseases beyond occasional benefit from glycine in muscle dystrophies and quinine in myotonia, attention must be given to the patient's mental hygiene These conditions usually progress inexorably

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## THE NEUROSES RELATED TO THE MANIC-DEPRESSIVE CONSTITUTION

FOSTER KENNEDY, M D, F.R S (Edin)\*

AT the outset of discussion one must define one's terms, the title of this chapter, "The Neuroses Related to the Manic-Depressive Constitution," must bring to mind almost as many different images as there may be readers

And the matter of the significance and emotional value of "words" will need consideration before the writing has ended, for it is certain that men do not live by bread alone, but mainly by catchwords What we *call* a thing becomes often in our conscious mind the thing itself, and the "word" can cease being what it truly is, a tool or a symbol of a thought, and grow into a god, or dwindle into a mere term of abuse

### WHAT IS A HUMAN BEING?

In the consideration of the disordered thinking or disordered acting in the neurotic, we have to consider first, and to some purpose, what we imagine a human being to be is he Soul-Body-Mind? is he Body-Mind? is he a Behavioristic Body?

Is He a Soul-Body-Mind?—This is mainly a theological concept, a trinitarian formula lacking physiology, but knowing well Man's dynamic drive The psychoanalysts have taken this formula of Soul-Body-Mind over, in a style curiously debased They have replaced Hope by Lust, the Soul by Libido, and Intellect by the so-called "dominant unconscious", all in the spirit of surrealism, fantastic and rigid Uneducated by their betters and forebears, they would make, scholastically, without however the discipline of the scholastic, a brave new world out of mud pies

Psychoanalysis has been the current style by which this great trinitarian idea has been presented to us But its theories are verbal, its "science" largely dogmatic assertions unsupported by anthropological research or by masters of education, and as Freud confessed in his last lectures, it has no true therapeutic value

One might pause a moment here to regard an identical movement which ran rampant through half of the last century Most of us think Phrenology so absurd as to be totally negligible, yet it furnished for more than two generations subject for debate in newspaper, lecture-room and theater Even men like Emerson and Oliver Wendell Holmes perforce had to consider it and refer to it in the Sixties It swam in a

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\* Professor of Neurology, Cornell University Medical College, Director, Neurological Department, Bellevue Hospital, New York City



sea of new words for old faculties "philoprogenitiveness" has survived through its comicality, its vogue was lifted and sustained by its claim "to tell your fortune,—and the kind of thing you are,"—and the most learned physicians were Chairmen of the Phrenological Societies, of which the Transactions can today be read by the curious in *The Lancet* of, say, 1830. This pseudo-science, this strumpet among the learned, served a good purpose, like many a strumpet. It was the gilded coach which carried Gall's great idea of cerebral localization of function along the corridors of the nineteenth century, that it might become known in the Seventies to men of the caliber of Hughlings Jackson, Hitzig, Munk and Ferrier. They, throwing away its nonsense laid truly, by dint of Gall's inspiration, the foundations of our modern knowledge of the physiology of the brain.

The solid contribution of Freud, when dug out of its clay, will prove probably as important as did that of Gall. For each individual, as he grows from the embryo to the adult, is a little cycle of the race. We have long known that from the egg to death we pass through stages in our body at least similar to those through which humanity has passed before. Freud has made it clear that in our emotions, in our urgings, in the preponderance of this feeling or instinct over that, at different periods of our lives, we have a like evolution, and—if we live into senility—devolution, of personality. He has shown the child as indeed no angel, but rather, at the age of five a polytheistic savage, having for his authority, and, too, his private pleasure, a genius loci in every tree and star, and at ten as a kind of Nazi who would naturally be characterized by restricted imagination, hypertrophied tribal emotions, and truculence towards other tribes, lie would be, and is regimented in ritual, totally intolerant, and—to offset his annoying sense of inadequacy—brutally contemptuous towards all those he thinks weaker than himself.

Freud has insisted that the child's sexual instincts emerge by gradual progression from an emotional preoccupation with one orifice of its body to an emotional preoccupation with another. However, Freud himself doubts the therapeutic value of this contribution to our knowledge of ourselves. But at least his teaching has made clear how our instincts have developed within the microcosm of each man's body. He has taught us, how—if inherited endowment be lacking by which to attain maturity—a man, or masses of men may stick at the different instinctual levels. However, as regards some of Freud's other conclusions, I feel that while, bodily, we have still vestigial remnants of our past, like gill slits and emotionally, others like sexual reversions, it is absurd to attempt to estimate the total adult body in terms of gill slits, or the total adult personality in terms of an uncovered sexual reversion.

Freud's work has served, then, to formulate what one might call

the phylogeny of personality and to make clear the stratification in growth of motivated desire, it has diagrammed, perhaps by oversimplification, how one emotion forms the basal matrix in the growing organism for the next emotion to be developed. It has thus unified our notions of character formation by making them analogous to the idea of anatomical recapitulation in each human organism, of the various physical stages through which humanity has passed, analogous also to the Jacksonian physiological demonstration of the nervous hierarchy, through which we see that patterns of ancient reflex behavior persist latently under the command of the last appointed controller—only to come out into the open when that control has weakened.

However, one must notice that the anatomist, appreciating the excellence of the persisting mechanisms in us of our early ancestors, appraises the whole evolved organism as more valid than are the traces of the primitive, and the Jacksonian neurologist regards cortical brain control more highly in a general way than the spinal ejaculatory reflex. Only the Freudian "psychoanalyst" reduces through a kitchen rebellion the total organism to its lowest and commonest denominator and would seek to explain its thoughts and behavior in terms, as I have just said, of its gill-slits and equally primitive sexual trends.

One sometimes wonders how the psychoanalysts justify the existence of a conscious mind at all! Possibly it is a contraption to be a psychoanalyst with!

**Is He a Behavioristic Body?**—This idea of man is not much more satisfactory than the one discussed. The Behavioristic School, deserted before its adolescence by its semi-parent, and chief sponsor, has shown less survival value than has Freudian dogma. Perhaps because it aspires less than Freud to tell, like palmistry, self-conscious little people more about themselves. It denies the substance of heredity and asserts roundly that "training" can make figs of thistles, and a silk purse from a sow's ear.

Once I heard the Half-Father of Behaviorism passionately deny the influence of heredity in human behavior and human structure. He said roundly and loudly to a great audience that "so far was he from believing in heredity, he was not prepared to admit, that if a human ovum and a spermatozoon were to unite outside the human uterus, the resulting organism would necessarily possess two eyes, a nose and a mouth." After ten seconds of stunned silence in the audience, a modest little man rose to assure the explodant that he "truly could have no idea the kind of pure town he was visiting, here in New York. He would assure him that if an ovum and a spermatozoon were even to *attempt* to unite on Broadway, they'd both be arrested by the police."

**Or Is He a Body-Mind?**—There remains Body-Mind—a dualism also of ecclesiastical origin. We know now, in the light of the New Physics, that matter, mind and structure are all the same thing—geometric pat-

terns of energy molecules, that we ourselves are, if you will, electrical aggregations of exquisite complexity and that our protoplasm is identical with our aim and purpose

But our *humanness* lies in that very complexity. By this not only can we temporarily capture energy for our use, but, by the *distilling* mechanism of our nervous system, we can transmute such primitive energy to conscious aspirations, abstract thought, and even into compassion for those about us. And our ability to do this well lies largely in the quality of brain and body which we have each been given.

#### WHO ARE THE NEUROTICS?

Time and Disease may each so injure our instrument of refining and distillation that the end product may be murky, uncertain and unhappy—and of these are the neurotics of whom we would speak here.

And we speak here as in a clinic, not expecting surely to reach conclusions on Human Reality in an hour and halt, so of what shall we speak? First, that "a neurotic," to quote from my first sentence, is not a term of abuse, that he is as real a thing as you or me. We might all properly say "And there, but for the Grace of God goes myself."

The jejune words "functional" and "organic" which in most speakers' minds mean "imaginary—yellow to be cuffed, and 'real—red blooded, to be cured" lame our thinking as did all the dualistic vocabulary of the Churches since the debate of Origen and Celsus. These two words, convenient as they are, obscure the question. One, "organic," refers to the "pathology of fiber" and the limitations of the microscope, the other, "functional," adumbrates the pathology of *forces*—which is the pathology of the future we, having been allowed to see wonderfully, have become blinded for all that cannot be seen. Further, to describe either, the patient must use words—and often these are employed not to explain, but to explain away lower happenings.

They Think, Feel and Act Unsurely—One must stress again the truly immaterial nature of man. Body-Mind is organized energy, each man organized by his inheritance into a frame of certain dimensions. Possessing, however, at the same time, certain growth possibilities. If exposed to environmental forces of culture, these can lead out of him by education all that he has. But no education can put *in* more than the educated possesses in ability to take in or to put *out*.

So the neurotic can, for many reasons, think unsurely, feel unsurely and act unsurely—and in moments of weakness nearly all of us can do these things.

Our individual complaints are vocalized according to the scope of our intellect, the range of our vocabulary, the inherited sensibility of our skin reactions and according to the innate or educated individual fortitude to which each of us has aspired and achieved.

Here, I'd ask each member of this clinic to spend one whole day

reading quickly—it is needless for our purpose to do it slowly—a number of psychiatric books There you'll find, for sure, uncertainty, evasion, verbalism, words replacing things and often ideas, jargon and jargonese, put in, not as old words re-used, but as new words made up These it would seem are meant to explain better, old things, old things, no one of which whole books could explain,—like "Censor" by which to replace "Conscience," like "Transference" to replace "Salvation," like all "Aspirations" abolished by "Libido" One gets lost in these weaving drifts of language which so obscure the outlines of the land one would see—and one suspects such drifting clouds may be smoke screens to hide the camouflage artist who puts them up

And, having spent our twelve hours on this task, we return now to our pattern of thinking, feeling, acting—unsurely

These three, thinking, feeling and acting, are, for everyday use, the total man—containing in "acting" the resultant also of the "organic" "unconscious," comprising those vast forces that determine, by no will of ours, that we should, for instance, breathe 18 to the minute, have our heart beat 72 times in the same space, keep our temperature steady in an arbitrary fashion despite surroundings and, strangest of all, lie unconscious for the hours of darkness while the earth turns round and about all of that we lack any personal experience or knowledge

For, and few think of this, we are the target and the object of forces, from inside ourselves and from without us, of which we have no conscious awareness, these build us, undermine us, deflect us, direct us, largely by as much as we have been equipped to accept, to resist, to rule the forces impinging on us and to determine direction and result in our thought and action

Obsessional Thinking—Please remember that no man in the world knows what is "sleep" I mean, we can describe sleep, we can discuss blood pressure, pulse rate, water balance and metabolism in sleep, but no one can say how the condition of sleep is brought about, or what it is

With such a huge gap in our facts—and we spend a third of our lives asleep—why should we expect to know precisely the reason why a few are obsessed by fear of dying, or by distress against uncleanness, by a persecution of jealousy, by a hatred of a friend with child, or by the fear of loss of fortune in a banker lest he may have put his name to a bit of paper he sees fluttering in the street Why should we know the exact mechanism of the persistence through adult life of the emotions of the—at that time quite normal—"magical" culture of the six-year old who must touch every third bar of a railing, who must jump over pavement cracks the child who at the same time is a superstitious poet and a witch doctor with obsessions! The six-year old who, by the imposition of his age is, just by his nature then, a Red Indian in culture and belief.

Yes, we do have notions and ideas by which we may—not explain—but deal with these things, but to describe events is not to explain them I remember in 1910, Dr August Hoch showing me in Manhattan State Hospital a woman whose right hand was paralyzed in both motor and sensory “hysterical” fashion Dr Hoch told me with satisfaction and almost triumph, “But of course, she’s distressed because of masturbation” I could not but reply, ‘Surely that’s no true answer She has only fulfilled the crude Bible command ‘if thy right hand offend thee, cut it off’ But why had she, so imperatively to do so? Millions of women do happily what she has disapproved of doing, and make themselves steadier thereby Why should she have to do in expiation what most of her sisters did not?’ It is not enough only to *describe* the symptom, except for temporary labeling We must ask ourselves why did *that* woman, and not the millions of other women have to substitute the “hand amputation” for the ‘hand action’ which had been unacceptable to her We may not get the right answer If however we do not ask ourselves such a question or, having asked it, give ourselves only a glib reply, we then have ceased to uphold science By that we satisfy ourselves with ourselves (and only quarter satisfied and sleeping poorly!) or we revolt against such untruthfulness become protestant in deed and word, and, knowing no answer, continue anxiously to seek one.

Thought certainly came before speech—look at any baby if you have not believed this It is therefore mere self protection to make wordy speech on our part take the place of thought! And how difficult for the patient to put into truly descriptive words errors in the autonomic organic unconscious

**Manic-Depressive Equivalents**—The patient’s descriptions may *not* be as an image seen in a mirror, his description in words may attempt to explain away, rather than to explain This factor doubtless enters into the manufacture of what I have called “manic depressive equivalents” where the underlying mood of depression may be denied by its owner and complaint be made only of a somatic symptom Through non-recognition, this type of case has received poor management by either misguided treatment or brutal dismissal

A woman of thirty-two years was referred to me as a case of “trigeminal neuralgia,” for which large doses of codeine trichlorethylene et cetera, had been given uselessly for over a year The symptoms were general constant aching pain in the face more on the left than right Also the pain was felt as “the base of the brain,” and was present too “across the forehead as a tight mental band” (a common translation of depression into somatic feeling) Sleep was disturbed, for she spent most of her time in bed and in a partial stupor from drugs “No the pain is so great I cannot interest myself in anything I sometimes feel better in the evenings” (again a characteristic of the diurnal rhythm of the manic-depressive constitution)

One became struck with the flat, unemotional facial expression, the personality looked drained away, only the eyes were anxious, with that apprehensive, rather hunted expression produced by raising the inner part of the eyebrows. She denied being depressed,—“but, of course, with this pain, I don’t feel very gay”—thus with an unhumorous “brave” little laugh.

The menstrual period had been very irregular during the time of her illness and had not appeared at all in the four months before examination.

Taking care not to refute the strongly held diagnosis of “trigeminal neuralgia,” I proposed to abolish the pain by what is usually called “electric shock treatment.” I call it “sleep by electric treatment.” And here I would like to pay tribute to the loyalty and openmindedness of her doctor, Dr. Mont Gross, who assented to this peculiar suggestion.

In three treatments she became well. In fact, she was symptom-free after the second,—nor, also characteristically, did she then say, “my pain has gone,” she simply looked young, happy, smiling, and at ease, and never referred to her pain at all. She remained perfectly well—in the family’s phrase, “on the top of the wave,” for eight months, then she was seized with a violent abdominal agony, which “made her roll on the floor.” Diet’s crisis was diagnosed, various treatments were given for two weeks in Florida. Pain was still “terrible” when I then saw her, and her face a dull, middle-aged nonentity. Finding no harmony in her somatic picture, the electric treatment was repeated with exactly the same result as before. Eight months went by. Lately she has been relieved in one treatment of a return, after another eight months’ interval of well-being, of the amorphous facial pain.

This patient has undoubtedly a manic-depressive mood swing with, as often happens, regular timing.

This cyclothymia with three cured episodes has been described in some detail, but many similar instances could be given.

One patient, a middle-aged woman, complaining of right-sided epigastric pain, had been treated from time to time throughout her life for recurrent duodenal ulcer. When depression had been ended, this symptom also evaporated.

Two cases of longstanding numbness and pain around the mouth and nose and teeth were cured in like fashion, they reminded one of the many depressive patients in whom one could know of the imminence of an attack by their sudden anxiety about their teeth, and their rather agitated complaints of queer pains about the hard palate.

Obsessive symptoms, however, can occur on other levels than the somatic.

A middle-aged woman rather quickly changed from being a cheery, efficient wife and mother, to being sleepless and tense, taciturn and mysterious. She muttered dark sayings about “that other woman,” and refused to believe her husband was really not “out on the town,” though he was obviously asleep in the house. She also lost her paranoid delusional system without comment, and resumed her normal ability to command the shop and household.

“Attacks” of obsessional thinking come to mind, about “names” and “numbers.” These often lasted for months at a time and were absent for periods of years between attacks. Those appearing in the past four

years have been ended by evaporating the "supersaturated solution" of depression out of which they'd been crystalized, prior to which the crystal had seemed—as always—more important than the 'fluid' from which it had emerged

Such forced resumption of old superstitious obsessions is as clear a return to a puerile pattern as is the reappearance of a forced grasping reflex which is normal in infants, in an adult with loss of high cortical control by perhaps frontal tumor or cerebral arteriosclerosis

These few descriptions concern persons who, for isolated periods in their lives, think unsurely, often delusionally, feel unsurely often as a protection against the social stigma of being thought insane, and under the whip of their delusions, whether these be in the realm of *ideas* or "*bodily*" *symptoms*, act unsurely

But what is common to them all? A *mood* of depression and anxiety, a sensation of such deep despair as to require explanation in "rational" or rather "acceptable" terms, compatible with the mores of their society, this to maintain a sense of integration in their own personality. Even those in whom no obsession no "pain" no delusion is crystalized, explain carefully that they are unhappy because they've been a bad mother to the four children," because 'the son is letting the sick man's "tailoring business go to pot," because, of course, of having in youth been guilty of the unpardonable sin 'Neither the husband's reassurance, nor the demonstration of books 'in the black' availed aught with the young mother, or the Jewish tailor of Paterson, New Jersey

In two depressions five years apart, a great financier whose relationship with a married friend had become accepted after eighteen years' duration, each time loudly blamed his "sin" for his condition. Always on recovery, he resumed his usual way of living. No argument that he had been ill in exactly the same pattern before he ever knew the lady ever penetrated the bulk-headed armor of protection which he built for himself

The layman always believes these rationalized tales and so do most doctors and very many psychiatrists "So and so went crazy from overwork," "from losing money in Wall Street" "from marrying the wrong woman" "So sad! So easily avoided if men were wise

Yet I have seen some of the people of whom I have just spoken go through as tragic experiences as can come to us, with fortitude and emotional ability, when such events occurred in their periods of well-being

What is this terrible recurrent depression which comes to so many in which early patterns of feeling and acting are forced upon the sufferers to be shrewdly explained away so often by dint of using in intellectual dishonesty their highest faculties of intellect and speech—and they do this, mark you in terror of the consequences the same people, sumably ourselves, would impose upon them

One observes that only rarely is but one case of such disorder registered in a single affected family, in a group of two or three generations. Most often, over that time, seven or ten persons so afflicted can be identified.

So, it must surely be a thing inherited, innate, and part of the organism itself. After all, if these states could be produced by environmental stress there should have been an epidemic of manic-depressive psychoses, during the last war of four years of terrific slaughter and strain. But there occurred no increase over the peacetime figures.

**What Is This Inner Wave, This Recurrent Built-in Pattern, This Rhythmic Flux?**—Consider that in the Universe everything exists by reason of its opposite, there can be no light without darkness, nor height without hollow, electricity is positive and negative, systole lives by diastole. Life, as we know it, depends on the balance of power in the organism. We live in health in the unstable equilibrium maintained by the energy tension of our accelerators, the sympathetic system, balanced by our brakes in the parasympathetic. Thus flexibility is gained, whereby environmental changes can be met so successfully that in health the adaptation does not even reach consciousness.

The balance in these forces is delicate, it can be changed, and in every degree. It varies in all of us, but so slightly that most of us stable fellows are hardly aware of those periods in which we are a bit glum, in which work tires us and we begin to waken at 4 in the morning, in which we put off the harder and the newer task, in which we allow ourselves to play with the dream of never trying again to climb the climbing wave, in which we ask ourselves, "Why should we toil, the roof and crown of things?"

Then one day by no discernible fiat, the sun shines better, the gilt again glints the gingerbread, we whistle in the shower and return with a happy hope to the job of work which for long we've wanted to do, but had, for almost as long, postponed.

Such rhythm is normal, all living things live on a pulse, but a good thing can always be overdone. Push the brakes harder and the machine slows down, metabolism is reduced, peristalsis slackens, weight increases, sex decreases, and in the perceiving centers there comes what is interpreted as a vast gloom.

The depression is often not "accepted" by the master of the house, but the sick feelings are resented. The doctor too often fails to understand the pathology of forces by which he is confronted.

Balanced health, this homeostasis as Cannon calls it, must be implemented. *It would seem certain that this control of power and pace is through or in the hypothalamus, the central governor of vegetative rhythm and, I believe, of emotional rhythm as well.*

**Illustrative Cases**—Let me put two or three cases before you, and please think of their implications.



Katherine M., now aged nineteen years, when she was nine was referred to me by Dr. St. Lawrence. She had fever, headache, stiff neck, at the beginning prolonged light stupor, double vision, and 68 cells in the spinal fluid.

Dr. Tilney and myself had no hesitation in diagnosing her case as encephalitis.

She was in bed for five weeks. When the stupor had cleared, peculiar behavior became manifest. The child, when perhaps sitting up in bed, would be seen within half-a-minute to have become largely immobilized. Her facial expression ceased to be animated, her eyes stared unwinkingly. She would then answer questions in a dull monotonous voice, often making mistakes in her answer to simple questions regarding her age and her address. During this phase she was capable of adding two and two or four and four but made mistakes, or she added quite irrationally without any evidence of thought, nine and four, seven and eight.

The limbs exhibited the waxy flexibility characteristic of certain catatonic states seen in "schizophrenia." The arms if placed in some grotesque and uncomfortable position would remain unsupported and apparently without fatigue, until they were either replaced or she was ordered sharply to put them down.

These episodes at first occurred several times a day and would last from five to forty minutes. They would end about as quickly as they had begun, that is to say, she would blink, rub her eyes, look animated, move about in bed, and perhaps then slip out of bed and run about the room with the childish gestures appropriate to her age. Asked what had been happening to her, she never could tell us more than that she "had felt queer and could not talk right."

After two months these episodes were occurring only occasionally when I ceased to see her, then she went to her home in the Middle West.

Some two years afterwards I heard from friends that she was very well but apparently very nervous. I was therefore not surprised when in September of 1941, I was again consulted because, ever since her original illness, she had been subject to a rhythm of fluctuating energy and emotion. This had settled into a constant pattern, nine to thirteen days of elation in which she would look very bright, was greatly animated, was very restless, rarely sat down and then only on the edge of her chair, had bursts of talk, did her lessons at top speed and far more than was required, and slept very little.

On many occasions she was known not to have slept at all for six days and nights, this without any sign of fatigue but with loss of weight.

At the end of this period of elation she would, inside one day, begin to slow up, quiet down, become shut into herself, answer in monosyllables in a low flat voice, work very slowly at her lessons, she would have the general air of a middle-aged faded nun.

This state would last from two to three weeks and was always followed by a period of elation such as has been described.

Clearly she was a manic-depressive with a very rapid mood swing of curious but timed regularity. (There was no history of emotional instability in her family.) For years she had made engagements according to the way she knew she would be when the engagement day came.

She had been unable to remain at boarding-schools because in her elated periods, she had kept all the girls in the dormitory awake by conversation all night and every night and would often insist at 3 in the morning on stilling her horse and riding across country.

I was of the opinion, in 1941, that by *electrical treatment* it was possible to cure the *episode*, but that the treatment had no prophylactic value for the future. I therefore did not think it would be advantageous

to administer this treatment to this patient and did not do so till the spring of 1942

She has received only five treatments, administered at the beginning of the elated period. They have always restored the normal rhythm of sleep, and produced tranquillity of emotion and behavior. No treatment has been given, or required, since April, 1943. She has been successfully maintained in boarding school, and her family report her better than she has ever been. In fact, since May of this year, the difference between her period of elation and period of depression could be detected only by members of her family who themselves said that perhaps they only saw anything unusual because they were naturally looking for trouble.

Another case was H. G., seen in consultation with Dr. Malcolm Goodridge in May, 1921. This patient served as a private in the United States Marines during the last war and was supposed to have disintegrated mentally following an alleged attack of influenza in London during the month after the armistice. He was placed in Bloomingdale Hospital for about eight months after his return home. The diagnosis was *dementia praecox*, at that time still the fashionable name for schizophrenia. The clinical picture seen in the spring of 1921 was sufficiently confusing, a young man of splendid physique carried his height of 6 feet 2 inches (188 cm.) with a pronounced stoop, an acquisition of his illness. Without syphilis, the pupils were distinctly sluggish to light, the right side of the face flattened in its creases, there was a fine jelly-like but definite nystagmus on lateral conjugate deviation of the eyes to the right or left. There was pronounced tremor in the extended hands. He had lost more than 30 pounds since his illness.

Except for the absence of the abdominal reflexes, great increase in the arm, knee, and ankle reflexes, and involuntary shivering movements of the pectoral muscles, nothing of pathologic interest could be made out in the sensori-motor system. He suffered, however, from severe nocturnal insomnia, rarely sleeping more than two hours before dawn, after which he would usually awaken and again grow drowsy and perhaps sleep, for three or four hours before noon. Whether he had slept or not, during the first part of the day he was utterly inert, and exasperated by his inertia. He had the utmost difficulty, through defective will power and indecision in accomplishing simple acts like shaving, dressing or bathing. He agonized for hours in futile efforts to write a short note or keep an important engagement during the early part of the day. In his mental attitude there was no trace of negativism, he desired passionately to do those things which he could not do at that time, and which later in the day he often could do with relative ease.

There was a distinct resemblance between his inability to perform acts to the completion of which he was urged by will, for which he lacked the stronger adjunct of emotion, and the palsy of purely voluntary movements in midbrain encephalitis of the parkinsonian type—palsies so often abolished by emotional stimulation. He complained frequently of "numb attacks" during which he felt "very cold," and in which he shivered and his teeth would chatter like a man with a rigor. During these attacks, even in July weather, his rectal temperature was always subnormal, on several occasions being 97° F., and on his skin were large patches of gooseflesh which covered a third of the body area at a time and which, under observation, changed their position like a breeze over still water.

In the same general period but not necessarily and indeed rarely at the same

hours, he had attacks of disturbed breathing rhythm of from a quarter to half a hour's duration. During these attacks he felt as though he could not fill his lungs with air (a frequent somatic symptom of depression and inner anxiety) and breathed with all his accessory respiratory muscles from fifty-six to sixty-four times a minute. At other times, he experienced what seemed like a spasm of the laryngeal muscles and breathed more and more stertorously and ineffectively so that the lips were cyanosed and the eyes protruded. Phenomena such as these have appeared at times in hysteria, and various physicians had considered them hysterical in this case. Such explanation, however, could not account for the patient's abnormal thirst for ice water. He consumed for a period of eighteen months between fifty and sixty tumblers of water every twenty-four hours and had proportionate polyuria.

An analysis of the initial illness in December, 1918, which the patient had always considered "influenza," revealed the only symptom to have been "severe headache and intense sleepiness by day and by night." Two negative features of value, however, were that he had had no feeling of fever and that he had never reported sick to a medical officer. It is highly unlikely that this could have been true of any youthful patient with the "influenza" which was really "cyanotic pneumonia" prevalent in London at the end of 1918. Furthermore, after three or four weeks, sleepiness disappeared during the night time and was present only by day—a reversal of the sleep mechanism sufficiently familiar to all students of epidemic encephalitis.

The patient's symptoms during the last eight months of his illness gradually improved to almost normal, with little or no morning inertia, no difficulty with respiration and no rigors, polydipsia was reduced to an intake of only three quarts of water a day.

A boy of fourteen years had a similar polydipsia and polyuria, tremors in the upper extremities, excessive salivation and similar distressing paroxysmal attacks in which breathing was exceedingly rapid, labored and difficult. At these times there was great emotional distress and suffering. The boy had acute encephalitis in January, 1920, with visual disturbance, diplopia, fever and excessive incontinence. This was followed for many months by apparent recovery and was gradually succeeded by a rhythmic incessant cough, and stammering of speech and thereafter by the distressing symptoms already described.

#### THE ROLE OF THE HYPOTHALAMUS IN MANIC-DEPRESSIVE RHYTHMS

The integrating mechanism of the diffusely working sympathetic and the discretely working parasympathetic are linked and may be activated by hormonal messengers chiefly from the hypophysis, through the two vascular systems carrying blood from the capillary bed of the posterior lobe to the capillary bed of the tuber and supraoptic nuclei. The hypothalamus is a neuroglandular instrument in control of vital rhythm. The timing of the organism is placed there: control of heart rate, of breathing, of water balance, of the cycle of sleep and constancy, of weight and temperature and the rhythm of the nervous

The ebb and flow in mood, behavior and the emotional expression follows stimulation or depression of these areas

Foerster produced the symptoms of acute mania when he set in motion a tumor pressing from below the walls of the third ventricle In another case, when he wiped blood from the third ventricle walls, manic excitement at once occurred

Ranson states that "the fact is no longer doubtful that a manic condition can be produced by mechanical stimulation of the oral part of the hypothalamus in man, and that these symptoms cannot be produced from any other spot "

On the other hand, interference with the posterior hypothalamus is followed by sleep and unconsciousness

The character of these hypothalamic rhythms is like our fingerprints, superficially identical, in detail utterly specific for each individual They would appear at first sight, to be under the control of the conscious ego, and influenced by surrounding conditions But so do the Atlantic rollers seem to be made by the wind and the weather These, however, only change the appearance of the top of the roller The great wave itself, propagating its energy for thousands of miles across the sea, is really made by another force of which the observer cannot be conscious, namely, the rotation of the earth

#### THE INSTABILITY OF MOODS

Change in the balancing of nervous energy is only occasionally massive, producing either total depression or total elevation of the whole organism Changes may be, not total, but fragmentary—just as *petit mal* is a fragment of the whole convulsive phenomenon, or a spasmed hand or spasmodic torticollis is a fragment of a general dystonia So, the unbalance between sympathetic and parasympathetic may operate on different integration levels, giving rise to circulatory asthenic symptoms here, and to disordered digestive processes there, all to be interpreted through a mist of fear and depression by the intellect, a recent arrival in command, uncertain in decision, using for expression the new tool of an inadequate vocabulary, and liable in crises to divebomb for an overdefinite answer to a magic level, laid down in childhood by the anxieties of two million years

So, the uncertainties of feeling, of thinking and describing, and of acting, come from unbalance in the forces by which we live, by which we are permeated, which we inherit

We each possess a prevailing mood—which may be inherently unstable or made so by exogenous disease That mood and its changes are interpreted by our conscious thoughts and described with the faltering and inadequate noises of speech

The psychologist makes much, in fact all, of "speech" His criteria is what he is told and he interprets this into such other terms as he

pleases—often under a smoky lamp. The physiologist leaves out subjective description and latent anthropological levels and interprets all in terms of reflexes or chemistry. The nutritionist snaps his fingers, and rightly enough, for attention to the accessory food factors and caloric values. But the wise observer must gather news from each expert. He will decide that the *mood* is the source of action—feeling and thought, is dominant and often unstable. In unstable periods the conscious mind often has no capacity for integrative action—misunderstands, explains badly, and runs for cover and help to a latent cultural level of thought and feeling.

To avoid these unhappy things, a man must first be well born and well fed. Good brain begets good mind. Then he must be well taught—to develop fortitude which includes independence, and humor which gives courage by a sense of proportion and an educated philosophy which, as the Greeks had it, enfolded all else. He must develop a personal integrity which knows itself to be without self-reproach or fear.

He will then be able to live with his innate emotional pattern without overmuch disturbance if the forces making the pattern remain in balance.

#### THE VALUE OF ELECTRIC THERAPY

For those whose pattern is hereditarily unbalanced, for those having good pattern but unfitted by education to live with it, or for those whose patterns have become diseased, help can sometimes be found only in the modern electric therapy.

As yet we use insulin, metrazol and electric sleep therapy to alter the balance of chemical and physical forces in a manner largely empiric. We know from thousands of cases that the passage of from 80 to 150 volts of electric current for a tenth of a second through the brain produces an often miraculous alteration for the better in mood and obsessive thinking, and that agitated depression—even though accompanied by a delusional state, can by this means be replaced by a happy tranquillity and clear-eyed insight, and further, that mood of elation and even mania grow quieted to a normal level.

How is this extraordinary result brought about? Clearly in the depressed cases the sympathetic is hugely stimulated; a balance between opposing energy forces is struck and normal rhythms reestablished—even those of sleep and menstruation are renewed.

However, only our five senses prevent us from perceiving that matter and mind are merely different forms of the same things. In truth we are geometric aggregations of force molecules, probably each with his individual pattern, derangement of which changes mood and the intramural radioactivity that we call thought. Why electric treatment should reestablish the normal energy balance and pattern rather than still further disturb it will no doubt be discovered—given Peace in our time.

So, our attitude is more a biopsychic approach than a mechanistic approach. We must believe that we cannot have intellect or ecstasy without a good neuronie endowment.

The strategic outlines and boundaries of mind are laid down by what we call physical heredity—its tactical plan by social inheritance, by education, and by the molding pressures of sex, the herd and hunger. All may be destroyed by infection, or injury or degeneration.

We are now only picking at the locks of doors behind which lie the answer to these mysteries. Many keys will be needed for the opening, but it surely will not be beyond man's wit to make them.

We have in this physical therapy an attack on mental illness which means to the treatment of disorders of the "mind" what the appearance of Lister's carbolic spray meant to surgery.

## CHRONIC ENDOCRINE DISORDERS

WILLARD O THOMPSON, M.D., F.A.C.P.\*

Most endocrine disorders are chronic in the sense that they commonly persist until specific treatment is carried out and those involving hypofunction of glands of internal secretion usually recur when specific treatment is omitted. It will, therefore, be impossible in the space allotted to cover in detail the whole field of chronic disorders of the endocrine glands. Emphasis will be placed on those disturbances with which the practicing physician is most often confronted.

### THE THYROID

**Hypothyroidism**—Once a deficiency of the thyroid develops, it usually persists throughout life and its manifestations will usually reappear gradually when the administration of desiccated thyroid is discontinued. The signs and symptoms that develop on omission of treatment are always similar in the same patient except in the case of cretinism. In this condition the administration of thyroid may produce such great changes in the patient that some manifestations of thyroid deficiency which follow the omission of treatment may vary at different ages in the same patient.

**Diagnosis**—Cretinism and myxedema are not commonly encountered by the average physician, with the result that the diagnosis is often not made until the disease has been present for a considerable

To the trained observer the diagnosis of full blown *myxedema* is not difficult. To the average physician, however, it presents some difficulty because of its rarity. It is still confused with chronic nephritis, particularly the nephrotic variety, with anemias of various sorts and with Simmonds' disease (pituitary' cachexia). It is sometimes confused with chronic nephritis because some older patients with myxedema may have hypertension, transient albuminuria and secondary anemia. The characteristic myxedematous facies is absent in chronic nephritis as well as the dryness of the skin, thickness of the tongue and slow, thick characteristic speech. Some patients with myxedema develop edema of dependent portions of the body and in some it may be extreme and result in marked ascites, thereby causing the disease to be confused with nephrosis in which the basal metabolism is also often very low. However, the concentration of serum protein is normal in myxedema, and there is no reversal of the albumin-globulin ratio as in nephrosis.

Some degree of secondary anemia is commonly present in patients with myxedema, and occasionally myxedema and pernicious anemia coexist in the same patient. The anemia per se, however, does not produce the clinical appearance of myxedema. It is usually necessary to give specific treatment for both anemia and myxedema in order to correct them. Occasionally patients with myxedema are thought to have a brain tumor because of the presence of ataxia and a high concentration of protein in the cerebrospinal fluid. The cerebrospinal fluid does not show other abnormalities. During the administration of thyroid the concentration of protein in the fluid promptly drops to within normal limits.

**TREATMENT**—Myxedema develops insidiously over a period of many years. Two serious errors may be made in treatment. (1) The initial dose of desiccated thyroid may be too large so that unpleasant and sometimes harmful effects are produced. There is great danger in older people of inducing a coronary thrombosis by the initial administration of too large doses. (2) Failure to continue treatment.

The treatment of primary hypothyroidism may be outlined as follows<sup>1</sup>

- 1 Administer the minimum amount of *desiccated thyroid* necessary to maintain a normal level of metabolism. The average dose required for maintenance in adult thyroidless individuals is from 1½ to 2 grains of USP thyroid daily (0.18 to 0.23 per cent iodine). The dosage for cretins is noted above.

- 2 Begin with a small dose (1 grain daily in adults) and increase gradually after several weeks until the correct amount is being administered.

- 3 Changes in the dose should be made slowly because of slow adjustment. At least two months is required for complete adjustment to any dose.



4 Avoid large initial doses in all patients, particularly in those with arteriosclerosis and coronary disease. In such patients the initial dose should not exceed  $\frac{1}{2}$  grain daily, and it may be necessary to adjust the metabolism at a slightly subnormal level because of the inability of the heart to meet the demands placed upon it by a normal level.

5 *Thyroxin* has no advantage over desiccated thyroid in the treatment of myxedema except in rare instances. Any attempt to correct the disease quickly by the initial administration of thyroxin intravenously not only may make the patient very uncomfortable because of muscle tenderness but may be very harmful. If an initial dose of desiccated thyroid is too large, muscle tenderness may be so great that the patient is unable to sleep.

From the standpoint of hypometabolism the problem that confronts the physician most is the matter of diagnosis and treatment in patients who have a moderate depression of the basal metabolism (from minus 15 to minus 25 per cent) but who do not appear to be myxedematous. In some of these patients there is present a mild hypothyroidism that is primary in type, in others there is a mild hypothyroidism that is secondary to a deficiency of the anterior lobe of the pituitary. In others the cause of the low metabolism cannot be determined at the present time. In many of them it is possible to determine the presence or absence of hypothyroidism only by a therapeutic test with thyroid. If the patient is improved when given the minimum amount of desiccated thyroid that is necessary to raise the basal metabolism to normal it may be assumed that some hypothyroidism is present and the administration of desiccated thyroid necessary. However, if the patient does not improve, its administration is futile and may even make the patient worse.

**Hyperthyroidism—Hyperthyroidism** once it appears commonly persists for years unless the disease is abolished by appropriate therapy. The intensity of the disease often varies in the same patient from time to time, particularly when it is of the exophthalmic goiter type. In some instances the remissions may be so great that the basal metabolism drops to a subnormal level and clinical evidences of hypothyroidism appear. This spontaneous substitution of the hypothyroid state for the hyperthyroid one may be followed by the reappearance of hyperthyroidism. Remissions and relapses may go on for years. In other patients the disease appears to remain in a steady state with approximately the same elevation of the basal metabolism persisting for long periods of time.

**Postoperative Thyrotoxicosis**—Of particular interest is the persistence and recurrence of toxic goiter following subtotal thyroidectomy. In many well run thyroid clinics the incidence of postoperative thyrotoxicosis varies from 5 to 15 per cent. Why the disease should be abolished in most cases by a subtotal thyroidectomy but not in others is

not entirely clear. In some instances inadequate removal of the thyroid plays a role, but in others rapid regeneration of thyroid tissue occurs in spite of adequate subtotal thyroidectomy. In some patients, records show that the disease is not completely abolished by three or four subtotal thyroidectomies. In such patients it would appear that the cause of the disease is acting with great intensity and is not eliminated by the thyroidectomy.

It should be pointed out that postoperative thyrotoxicosis usually represents a persistence of the disease and only occasionally a recurrence. This means, of course, that once the basal metabolism drops to within normal limits following the thyroidectomy and remains there for as long as one month when the patient is not receiving iodine, it is unlikely that the patient will ever be thyrotoxic again. In rare instances a recurrence may be observed months or years after the operation. Thyrotoxicosis following subtotal thyroidectomy behaves in the same manner as the untreated disease and is characterized in some patients by remissions and relapses. The management of the condition differs only slightly from that of the untreated disease.

**TREATMENT**—In most instances it is desirable to perform a *subtotal thyroidectomy* after adequate preparation of the patient. In a few others it may be possible to maintain the basal metabolism within normal limits by the administration of iodine until the disease disappears. It should be pointed out that the danger of complications, notably recurrent laryngeal nerve paralysis and parathyroid tetany, is much greater with the second and third than with the first thyroidectomy. In some instances in which one vocal cord is paralyzed and most of the palpable thyroid tissue is present on the opposite side, it may be desirable to use roentgen-ray therapy instead of resorting to further surgery. In general, however, the treatment of toxic goiter by irradiation of the gland is a very unsatisfactory procedure.

Of great interest are recent experiments on the control of toxic goiter by nonsurgical methods, particularly by the use of *radioactive iodine* and by the administration of *thiourea* and *thiouracil*. Sometimes during the prolonged administration of the thyrotropic factor of the pituitary, the basal metabolism will drop to within normal limits after an initial rise. There are many reasons for believing that the treatment of toxic goiter will eventually be accomplished by medical and not surgical procedures. However, these recent observations are still in the experimental stage and the best routine method of managing the disease still remains the performance of a subtotal thyroidectomy after adequate preoperative preparation of the patient.

#### THE PARATHYROIDS

Hypofunction and hyperfunction of the parathyroid glands are not very common and when they develop are usually cared for in special

clinics. However, both conditions may be encountered by any practicing physician. He must, therefore, be somewhat familiar with their signs and symptoms.

**Hypoparathyroidism (Tetany)**—Hypofunction of the parathyroids in most instances follows the removal of the parathyroid glands at the time of a thyroidectomy. It occasionally follows the removal of too much parathyroid tissue during a parathyroidectomy for hyperparathyroidism. In rare instances, a spontaneous form of the disease is seen which corresponds to spontaneous myxedema. The disease may vary greatly in severity, depending upon the extent of hypofunction. Acute and chronic forms are observed. Acute manifestations of the disease are noted when the function of the parathyroids is suddenly withdrawn, as following a parathyroidectomy. As time goes on, one of two things may happen. Some regeneration of parathyroid tissue may occur so that the hypofunction may be partially or completely relieved. It is more common for some degree of hypofunction to persist. The body gradually adapts itself to the loss of parathyroid function so that the symptoms of the disease in its chronic form are not so severe as in the acute form.

**DIAGNOSIS**—The most important *clinical signs* of tetany are numbness and tingling of the extremities, which may or may not be accompanied by pain, the signs of Chvostek and Trousseau, lowering of the concentration of calcium in the serum, and increase in the concentration of phosphorus while the phosphatase remains normal. The excretion of both calcium and phosphorus is low in the urine and normal in the stools. Erb's phenomenon, which is caused by increased nervous excitability, can be elicited only by special equipment which is rarely used in the practice of the average physician.

In general, the intensity of signs and symptoms is proportional to the degree of lowering of the concentration of the serum calcium, although there are exceptions to this rule. Occasionally a patient with extreme lowering of the calcium value will suddenly develop tetanic convulsions without showing either a Chvostek or a Trousseau sign and without complaining of any numbness. However, hypoparathyroidism is almost always detected before it progresses to the state of tetanic convulsions and no patient should die at the present time from parathyroid tetany. In general, it may be said that the development of convulsions in this disease indicates poor management.

The signs and symptoms of tetany usually do not develop until the concentration of calcium in the serum drops to about 7.5 mg. per 100 cc., although the actual level varies somewhat from patient to patient. In most patients with complete hypoparathyroidism the concentration of calcium drops to between 4 and 5 mg. per 100 cc. It should be emphasized that the determination of the serum calcium is not very valuable unless it is accompanied by the determination of the

concentration of the serum protein. About one half of the calcium in the serum is bound by protein and it is the ionized or diffusible calcium that is of primary importance in tetany. For this reason, the concentration of calcium in serum may be low without any symptoms of hypoparathyroidism being present. This phenomenon is seen in patients with nephrosis.

**COMPLICATIONS**—The most serious complication of untreated hypoparathyroidism is the development of bilateral *cataracts*. These do not seem to appear except in the more marked forms of the disease, and they do not appear at all if adequate treatment is given. It is, therefore, very important in treating patients with tetany to be sure that the treatment is adequate to maintain the calcium in the serum within normal limits and that the eyes are examined periodically to make sure that cataracts are not developing.

Some *spasm of the vocal cords* may be present in patients with parathyroid tetany. This is particularly evident in patients who have paralysis of at least one vocal cord. The same operative procedure that results in injury to the parathyroid glands may also result in injury to one of the recurrent laryngeal nerves. Consequently the association of parathyroid tetany and unilateral vocal cord paralysis is a common one. The symptoms produced by the paralysis are aggravated by the spasm resulting from parathyroid tetany.

**TREATMENT**—In treating the chronic form of the disease, parathyroid extract is not used and it is rarely used at the present time in the acute stage immediately following operation. The following procedures have proved most useful for prolonged management. (1) Administration of from 45 to 90 grains of *calcium lactate* or *calcium chloride* per day. This is administered in three equal doses. The first one is given with breakfast, the second about the middle of the afternoon and the third at bedtime. (2) Administration of some material that promotes the absorption of calcium from the gastro-intestinal tract. The best material for this purpose is *dihydratachysterol*, which is given in doses of 1 cc. two to four times per week. Large doses of vitamin D<sub>2</sub> such as 50,000 USP units daily are also of value but perhaps not quite as effective as dihydratachysterol. The object of treatment is to maintain the level of serum calcium within normal limits (9 to 11 mg. per 100 cc.). As a rule, when the patient feels well, the concentration of calcium is normal but this is not necessarily the case. The disease cannot be managed satisfactorily without laboratory facilities for determining the concentration of serum calcium. This is a comparatively difficult determination technically and the results obtained in many laboratories are often fictitious.

**Hyperparathyroidism**—Hyperparathyroidism is a rare disease, although a considerable number of cases have been reported in some

special clinics. It is usually present for years before it is recognized and is often detected only after serious damage is done to the body. In most instances it is not discovered until there have developed multiple bone cysts (*osteitis fibrosa cystica*) spontaneous fractures collapse of the vertebrae, renal calculi or giant cell tumors. The damage done by collapse of the spine cannot be repaired and chronic nephritis may develop in the more chronic cases of renal calculi.

**DIAGNOSIS**—Hyperparathyroidism should always be thought of in patients with unexplained muscle weakness, hypotonia, lack of appetite, nausea, constipation, pain in the bones and polyuria. The most important diagnostic sign is the presence of a high concentration of calcium in the serum. The concentration of phosphorus is low and that of the phosphatase is high. The excretion of calcium and phosphorus in the urine is high but normal in the stools. The diagnosis usually can not be definitely established by laboratory procedures unless the concentration of calcium in the serum is 12 mg. per 100 cc. or more. Careful roentgen ray examination of the skeleton is important although thinning of the bone and the development of multiple bone cysts may be prevented by the drinking of large quantities of milk. It is wise to make serum calcium determinations in all patients with renal calculi, particularly in those with recurrent stones.

Nodules may often be palpated in the region of the thyroid although they are usually not as large as thyroid adenomas. However they may sometimes be very large and they vary greatly in position. All of the parathyroid tumor is sometimes in the mediastinum just as in the case of some thyroid tumors.

**TREATMENT**—Treatment consists in the removal of an adequate amount of parathyroid tissue. Certain practical difficulties are encountered in this procedure. The number of parathyroid glands varies from one to fourteen and it is not always easy to find the offending gland or glands. An effort should always be made to determine where the parathyroid tumor is and to confirm the diagnosis by frozen section at operation and then to perform a subtotal parathyroidectomy. The development of parathyroid tetany after operation is common but this condition may be only temporary.

Following operation the concentrations of calcium and phosphorus in the serum usually return to normal fairly promptly, but the concentration of phosphatase becomes normal more slowly. In order to replace the calcium and phosphorus which have been lost from the skeleton, it is desirable to administer large quantities of these minerals as well as an adequate amount of vitamin D for many months. The objects of treatment are to prevent permanent damage to the skeleton and to prevent the development of renal calculi and chronic nephritis.

## ANTERIOR PITUITARY

The most important of the chronic diseases of the anterior lobe of the pituitary are dystrophia adiposogenitalis (Frohlich's syndrome), Simmonds' disease, chromophobe adenoma, dwarfism, acromegaly and pituitary basophilism (Cushing's syndrome)

**Dystrophia Adiposogenitalis**—The term "dystrophia adiposogenitalis" is a general one which applies to the disease in both children and adults, whereas the disease in children is known as the Frohlich syndrome. This condition is characterized in the male by obesity, hypogonadism and genu valgum. The shoulders are narrow, the breasts full, the abdomen large with a characteristic transverse fold just above the pubic area, the hips are broad and the forearms and lower extremities are often not much increased in size in contrast to the great excess of weight in the middle portion of the body. In only a few of the patients is cryptorchidism present. In the female the breasts may be poorly developed, one may be larger than the other or they may be normal in size but contain an excessive amount of fat tissue. The disease is sometimes but not very often associated with dwarfism, particularly if a pituitary tumor is present. In most instances the sella turcica is normal in size.

In some patients of this type, a complete transformation will occur at the time of puberty without treatment. In others, the condition persists throughout life. The diagnostic criteria are inadequate at present.

**TREATMENT**—It is probably wise to carry out treatment in all individuals in whom the hypogonadism is marked. It should be started between the tenth and twelfth years and continued until epiphyseal union is completed. *In the male*, the treatment consists of the administration of from 500 to 1000 international units of chorionic gonadotropin three times weekly. Sometimes with the administration of this material alone, complete transformation of the body contour occurs and no other form of therapy is necessary. In others, it may be necessary to supplement this form of therapy with a weight-reducing diet, and if the basal metabolism is low, with the administration of desiccated thyroid. *In the female*, the administration of chorionic gonadotropin does not appear to be as effective as in the male and in the more marked forms of the disease it may be necessary to use female sex hormone to influence skeletal molding and induce sexual maturity.

When the disease is not detected until later in life, a considerable amount of improvement may be produced in men by the administration of chorionic gonadotropin and a weight-reducing diet as above noted. However, the skeletal contour cannot be affected. In women, gonadotropic substances are not notably effective and as a rule some form of estrogenic material must be used.

**Simmonds' Disease**—Simmonds' disease or *pituitary cachexia* is a rare disorder in which there is a complete loss of all functions of the

anterior lobe of the pituitary, commonly following an infection. It is characterized by extreme weakness, loss of weight, lowering of the basal metabolism, lowering of the concentration of sugar in the blood (which may be so extreme that hyglycemic convulsions occur), loss of memory, anemia and hypogonadism with loss of sex function

The disease is often confused with anorexia nervosa and most patients that have been reported to have Simmonds' disease have probably actually suffered from anorexia nervosa. Patients with Simmonds disease appear seriously ill whereas those with anorexia nervosa appear comparatively well in spite of the extreme loss of weight

Some improvement may be produced in Simmonds disease by the correction of the hypogonadism with suitable gonadotropic material or sex hormone, by correcting the hypothyroidism and by administering a high caloric diet.

**Chromophobe Adenoma**—The chromophobe cells are inert and chromophobe adenomas are therefore commonly associated with underfunction of the pituitary, particularly when they are large enough to compress or replace the normal tissue. They vary greatly in size and the symptoms associated with them usually persist until adequate treatment is carried out.

**DIAGNOSIS**—The symptom complex depends upon the degree of loss of pituitary function and upon the presence or absence of pressure on the structures above the sella turcica notably the optic chiasm and the hypothalamic area of the brain.

*Signs and Symptoms Related to Underfunction of the Anterior Lobe of the Pituitary*—1 Hypothyroidism (secondary) The basal metabolism may drop to as low a level as in patients with complete absence of thyroid function, namely minus 40 to minus 50 per cent, but the clinical picture is different from that seen in myxedema. The rough, dry, scaly skin and the typical myxedematous facies are absent. The skin is usually smooth and soft and the hair is of fine texture.

2 Hypogonadism (secondary), with atrophy of the genitalia azoospermia and amenorrhea

3 Change in sugar metabolism with flattening of the sugar tolerance curve and a reduction of the fasting blood sugar

4 Obesity is commonly but not necessarily associated with the condition. When present it may be related to a disturbance in the base of the brain.

*Effects of Pressure on the Optic Chiasm*—The most common effect of pressure on the optic chiasm is a bitemporal hemianopia which at first involves the upper quadrants and later becomes complete. Finally the whole optic nerve degenerates and blindness ensues. The tumor may, of course, grow laterally and compress only one optic nerve producing a contralateral homonymous hemianopia. When the tumor breaks through the dural diaphragm it may encroach on the floor of

the third ventricle, producing various symptoms. In some instances it may extend far enough to block the third ventricle, therefore producing an internal hydrocephalus. In rare instances it may compress the third, fourth and sixth nerves, producing an extra-ocular palsy or it may invade the temporal lobe, producing uncinatc seizures.

**TREATMENT**—The symptoms associated with chromophobe adenoma of the pituitary usually persist throughout life unless specific treatment is given. In some patients definite improvement may follow *removal* of part or all of the adenoma, or release of the cystic fluid which it may contain. Such improvement is probably related to removal of pressure from the normal pituitary cells. Surgical intervention is indicated only when the tumor extends through the roof of the sella turcica and invades the structures lying just above it, particularly the optic chiasm. Roentgen ray therapy is of little value in this condition.

It is necessary to treat the hypopituitarism regardless of whether or not surgical measures are indicated. This is best done by treating the glandular hypofunctions that are secondary to the hypopituitarism, inasmuch as there is no pituitary extract that is very effective clinically. Great improvement may follow the treatment of the hypothyroidism with *desiccated thyroid* and the treatment of the hypogonadism with *stimulation* or *substitution therapy*. As obesity is commonly an associated condition, administration of a suitable weight-reducing diet may constitute an important part of the treatment.

**Dwarfism**—Pituitary dwarfism may persist indefinitely because there is no preparation of the growth factor of the pituitary that has much effect in man. It may be associated with a chromophobe adenoma, or no tumor may be present at all. The deficiency of growth factor must develop during the active growth period in order for dwarfism to result. All degrees of the condition may be noted, depending upon the severity of the pituitary deficiency and the age at which it begins. It is commonly associated with a deficiency of other functions of the pituitary, notably the thyrotropic and gonadotropic functions, but this is not necessarily the case. Growth factor is produced by the eosinophilic cells and the gonadotropic factor by the basophilic cells. It is therefore possible to have a pituitary dwarf with normal development of the genitalia and normal sex function, just as it is possible to have the reverse condition, namely eunuchoidism secondary to a deficient production of gonadotropic factor in an individual who is normal in height and whose pituitary therefore produces an adequate amount of pituitary growth factor.

**TREATMENT**—Although preparations of the growth factor are not particularly effective clinically, a considerable amount of skeletal growth may be induced in the male pituitary dwarf by stimulating the testes to produce male sex hormone, with *chorionic gonadotropin* or by the administration of *male sex hormone* itself. In order for this



material to produce its maximum effect, treatment must be started not later than the age of ten to twelve years. The amount of skeletal growth that can be induced in this manner is limited and if the dwarfism is extreme the skeleton will never achieve normal height regardless of the age at which treatment is started.

**Acromegaly**—Acromegaly is a disease of long duration. There are instances on record in which it has lasted for fifty years. It is usually caused by an eosinophilic adenoma of the pituitary, although it may be the result of hyperplasia of the eosinophil cells without the presence of an adenoma. The disease is rather frequently associated with overproduction of the thyrotropic factor and overproduction of the diabetogenic factor, so that syndromes resembling exophthalmic goiter and diabetes mellitus respectively are produced. The high basal metabolism in this condition shows some reduction during the administration of iodine and the diabetes is controlled with insulin just as it is in patients who do not have acromegaly.

**DIAGNOSIS**—There is little difficulty in making a diagnosis when the disease is well advanced. There is overgrowth of all the tissues in the body resulting in characteristic changes in the face, hands and feet. It is not often that the diagnosis is made in the early stages.

**TREATMENT**—The size of the sella turcica varies greatly but the adenoma is rarely large enough to demand surgical intervention, the only indication for which is pressure on the optic chiasm or on the floor of the third ventricle. In rare instances all the characteristic manifestations of invasion of the hypothalamic area may ensue. Unless surgery is indicated, *roentgen ray therapy* is the treatment of choice. This form of therapy is unsatisfactory and it is very difficult to tell when the disease is quiescent and when it is progressive. Skeletal changes may increase in spite of the presence of a normal level of basal metabolism and the absence of diabetes.

In some patients, severe headache is a very prominent feature and it may be very refractory to treatment. Chronic hypertrophic arthritis and renal calculi are not uncommon complications of acromegaly.

**Pituitary Basophilism (Cushing's Syndrome)**—A few years ago Cushing described a disease characterized by the following manifestations: obesity, hypertension, glycosuria, purplish striae in the abdomen, thighs and chest, hypogonadism (with amenorrhea in the female), hypertrichosis, weakness and increased excretion of nitrogen in the urine. The condition is commonly fatal although the patients may live for several years. According to Cushing's interpretation the disease is the result of a basophilic adenoma of the pituitary which is a microscopic in size. Other investigators have claimed it to be the result of an adenoma of the adrenal cortex which is found in a fairly large percentage of the patients.

**TREATMENT**—Some improvement has been reported in a few cases

stances following irradiation of the pituitary and following removal of basophilic adenomas of the pituitary and adenomas of the adrenals. Improvement has also been reported following the administration of male sex hormone, which causes storage of protein.

### THE POSTERIOR PITUITARY

**Diabetes Insipidus**—Diabetes insipidus is a rare disease but is occasionally encountered by the general practitioner. There are many reasons for believing that it is the result of a lesion in the base of the brain above the pituitary and not directly the result of a lesion in the posterior lobe itself.

Diabetes insipidus is characterized by excessive polydipsia and polyuria, with the passage of as much as from 12 to 14 liters of urine per day. The urine is of necessity of low specific gravity and water is eliminated from the body almost as fast as it is absorbed. The hormone of the posterior pituitary has some direct action on the kidney which results in the retention of water.

In rare instances the disease may be associated with hypofunction of the anterior lobe, with or without a pituitary tumor, although diabetes insipidus is not a common accompaniment of disturbances of the anterior lobe. The symptoms of the disease depend upon what involvement, if any, there is of the anterior lobe and of the hypothalamic area. The patients may be thin or obese.

**TREATMENT**—The disease is best treated by the *insufflation of desiccated posterior pituitary powder* into the nasal cavities. This procedure must be carried out six or eight times during the day in order to promote fairly continuous absorption. Two principles have been isolated from the posterior lobe, one having pressor and water-retaining properties (pitressin) and the other having oxytocic properties and causing the contraction of smooth muscle (pitocin). In actual practice, pitressin is rarely used in the treatment of diabetes insipidus.

### THE ADRENALS

**Addison's Disease**—The most important chronic disorder of the adrenals is Addison's disease, which invariably persists once it develops. It is caused by tuberculosis of the adrenals in about half of the patients and by atrophy in most of the remainder, resulting in destruction of the adrenal cortex. Without treatment, the disease is characterized by remissions and relapses and a gradual downhill course. The patient finally dies in a relapse or crisis from six months to fourteen years after the onset.

**DIAGNOSIS**—Among the more important manifestations of the disease are the following: (1) brownish pigmentation of the skin and buccal mucosa, (2) weakness, (3) loss of weight, (4) hypotension, (5) anorexia, nausea and vomiting, (6) reduction in the concentration of

sodium, chloride, carbon dioxide and sugar in the serum, (7) increase in the concentration of potassium and nonprotein nitrogen in the serum, and (8) increased excretion of sodium and chloride in the urine

In a crisis all of the signs and symptoms of the disease are exaggerated but the most outstanding manifestations are nausea, vomiting and hypotension. Nausea is always to be regarded in the most serious manner and means that adequate treatment must be instituted at once

TREATMENT—A crisis is treated as follows

- 1 Administration of from 10 to 40 cc. of adrenal cortex extract intravenously every hour
- 2 Intravenous administration of 5 per cent dextrose in Ringer's solution at the rate of 1 liter in eight hours

If desoxycorticosterone acetate has been used in treatment the daily dose is continued throughout the crisis and supplemented with the forms of therapy just described. As nausea subsides the patient is given food and fluid by mouth and the dose of cortical extract is gradually reduced. The patient is finally put on a *maintenance program* which may consist of any one of the following procedures

- 1 Subcutaneous administration of from 10 to 40 cc. of adrenal cortex extract daily in divided doses.
- 2 Subcutaneous administration of smaller amounts of adrenal cortex extract supplemented by sodium salts.
- 3 Subcutaneous implantation of pellets of desoxycorticosterone acetate (the initial implantation usually does not need to exceed 450 mg.)
- 4 Daily intramuscular injection of desoxycorticosterone acetate in a dose of from 5 to 20 mg.
- 5 A combination of smaller doses of desoxycorticosterone acetate and sodium salts.

The best results are obtained with large doses of adrenal cortex extract without supplementary salt therapy, but this form of treatment is very expensive

In a few patients the response to desoxycorticosterone acetate is unsatisfactory. Among the complications of its use may be mentioned generalized edema and hypertension, focal necrosis of the heart muscle, sudden death from myocardial failure and flaccid paralysis of the extremities. A few patients cannot tolerate this material and must therefore receive adrenal cortex extract. When it is effective, the most economical and time saving method of administration of desoxycorticosterone acetate is in the form of pellets placed in the subcutaneous area. One implantation lasts from six to nine months.

Desoxycorticosterone acetate affects the metabolism of sodium and potassium but does not have any effect on sugar metabolism. Corticosterone does affect both functions, while compound I affects primarily the sugar metabolism.

Patients with Addison's disease are particularly susceptible to the development of upper respiratory infections, and every infection is to be regarded seriously because it appears to increase the demands placed upon the adrenal glands. With adequate treatment, it would appear possible to keep these patients alive for many years.

### THE OVARIES

The problem of most importance is that of hypofunction. For an intelligent understanding of deficient function of the ovaries and testes certain general principles must be borne in mind. An intimate relationship exists between the anterior lobe of the pituitary and the gonads. Gonadotropic materials are produced in the pituitary which influence ovarian and testicular function. A follicle-stimulating principle stimulates the growth of the graafian follicles in the ovary and influences the function of the seminiferous tubules in the testis. A luteinizing principle causes luteinization of the developing follicles in the ovary and stimulates the interstitial cells in the testis.

Hypogonadism may be primary or secondary, depending upon whether or not the defect is present in the gonads or elsewhere, notably in the anterior lobe of the pituitary. In a similar manner, hypogonadism may be treated either by stimulating the gonads with suitable gonadotropic material or by substituting for it with the appropriate sex hormone. The type of treatment used depends upon the type of hypogonadism present and upon the activity of the therapeutic agents available. Most cases of hypogonadism appear to be secondary in type.

Three varieties of gonadotropic material are available for *stimulation therapy*:

- 1 Pituitary gonadotropin prepared from the pituitary itself
- 2 Equine gonadotropin prepared from the serum of the pregnant mare
- 3 Chorionic gonadotropin prepared from the urine of pregnant women (arises from the chorionic villi of the placenta)

Pituitary and equine gonadotropin are theoretically desirable as stimulating agents because they contain both follicle-stimulating and luteinizing material. In actual practice they are not especially effective. Chorionic gonadotropin is luteinizing in nature and is very effective in stimulating the interstitial cells of the testis, and therefore, in the treatment of secondary hypogonadism in the male. It is not especially effective in the female, and in the male it has the disadvantage that it does not stimulate spermatogenesis. The status of stimulation therapy in the female is not satisfactory, and in many instances in which this form of treatment is indicated, substitution therapy must be used because effective stimulating agents are not available. Very active preparations of the male and female sex hormones are obtainable in the form of testosterone propionate and various esters of estradiol, respectively.

**Secondary Hypoovarianism**—Stimulation therapy is theoretically indicated in all cases of hypoovarianism which are secondary to *hypopituitarism*. This abnormality is seen most commonly in women who have scanty or delayed menstruation, or both. The intermenstrual periods are usually prolonged and menstruation may be completely absent. Obesity is usually but not necessarily present. The external genitalia and the uterus may be poorly developed or they may be normal in size. The breasts are commonly within normal limits but the areolae and nipples are pale and poorly developed or atrophic. Axillary and pubic hair may be scanty.

**TREATMENT**—It is always wise first to try stimulation therapy with *pituitary* and *equine gonadotropin* and then resort to substitution therapy with *female sex hormone* if the former are ineffective. If substitution therapy is used, it is wise to combine it with *progesterone* in such a way as to reproduce the hormonal changes that occur during the normal menstrual cycle. This may be done in many instances by administering 1.66 mg. of estradiol benzoate intramuscularly twice a week for three weeks, although the effective dose varies in different patients. One day after the last dose, the daily administration of 10 mg. of progesterone is begun and continued for three days. Menstruation will usually set in within two to five days after the last dose of progesterone. The course of treatment may then be repeated.

In a few patients, scanty and delayed menstruation is caused by *hypothyroidism* and may be corrected by the administration of desiccated thyroid alone. Occasionally in patients with amenorrhea who are very obese, menstruation will appear at regular intervals following great loss of weight.

**Primary Hypoovarianism**—Substitution therapy is indicated in primary deficiencies of the ovary, notably in the menopause and in some cases of sexual immaturity. When the ovaries fail to function during the period of puberty, a syndrome develops that resembles the eunuchoid state in the male. Secondary sex characteristics do not appear, the breasts remain undeveloped, the external and internal genitalia remain infantile, little if any axillary and pubic hair appears, menstruation does not set in and skeletal disproportions are evident, the trunk being short and the extremities long although the total height of the body may be within normal limits.

**TREATMENT**—Following the administration of suitable dose of *female sex hormone* (from 1.66 mg. to 5 mg. of estradiol benzoate or dipropionate once or twice a week) to such a woman development of the secondary sex characteristics is noted with enlargement of the breasts, growth of the labia minora and uterus, gain in weight of from 15 to 20 pounds, increase in strength and development of a normal emotional status. Similar changes are induced by *stilbestrol*. If uterine bleeding appears at irregular intervals but may be brought to

regularly by combining the administration of estrogenic material with progesterone in the proper manner

**The Menopause**—The menopause is one of the major glandular problems that confront women. The symptoms vary greatly in intensity and duration, although it is not uncommon for them to last for several years. They are completely controlled by the administration of some suitable form of *female sex hormone* such as estradiol benzoate or dipropionate. The effective dose varies from 1.66 mg to 5 mg every seven to fourteen days, by intramuscular injection. The synthetic estrogen, stilbestrol, is highly effective and possesses the advantages of cheapness and of being active when administered orally. It is important to administer the minimum amount that will control symptoms. The effective dose varies from 0.33 to 1.5 mg daily in most patients.

One of the serious complications of estrogenic therapy is the production in some women of abnormal and excessive bleeding. This is most likely to occur in patients with fibroids, particularly when large amounts of estrogenic material are used. Women with fibroids must be treated with the greatest caution, and it is important in all instances not to overtreat the patient.

In the treatment of ovarian deficiencies of all types, it is essential that the patient be examined frequently and that the endocrinologist work in close cooperation with the gynecologist.

### THE TESTES

The most important chronic endocrine disorders of the testes are the primary and secondary types of male hypogonadism, the secondary type being the more common. Examples of this are the Frohlich syndrome and chromophobe adenoma of the pituitary described above and also some cases of undescended testes in which the primary defect appears to lie in the anterior lobe of the pituitary. Chorionic gonadotropin is effective in the treatment of these conditions and is commonly employed in a dose of from 500 to 1000 international units three times per week.

**Eunuchoidism**—Eunuchoidism may be primary or secondary and is usually associated with bilateral cryptorchidism, although very small atrophic testes may be present in the scrotum. The condition is characterized by poor development of secondary sex characteristics and by certain skeletal disproportions, notably a short trunk and long extremities. Eunuchoidism may vary in degree, depending upon the amount of function of the testicular tissue. Eunuchism represents complete loss of testicular function from inflammation, trauma or total ablation of the testes.

**Treatment**—In some cases of eunuchoidism, stimulation therapy may be effective, although in the majority, treatment with *male sex hormone* is indicated in a dose of from 25 to 50 mg administered intra-

muscularly three times a week. Striking changes occur with this material. In sexually immature men all the secondary sex characteristics will develop, including growth of the genitalia, prostate and body hair, lowering of the pitch of the voice and development of the musculature. All of the symptoms of eunuchoidism are completely alleviated by this form of therapy. The skeletal disproportions cannot be corrected after the age of puberty.

**Male Climacteric.**—In a few men a condition known as the male climacteric occurs after the age of forty-five years. It is very much less common than the menopause in the female, although the symptoms are similar. It is relieved promptly by the administration of male sex hormone. Great care must be exercised in arriving at the diagnosis in order not to overlook any serious organic disease.

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# THE TREATMENT OF GRAVES' DISEASE WITH SEVERE EXOPHTHALMOS

WILLIAM T. SALTER, M.D., F.A.C.P.\*

AND

MAYO H. SOLEY, M.D.†

## HISTORICAL INTRODUCTION

ALTHOUGH its etiology has not been established, Graves' disease is regarded as a well understood syndrome by most clinicians. The easy establishment of the diagnosis coupled with the development of relatively safe methods of subtotal destruction of the thyroid by means of surgical ablation or roentgen therapy together have resulted in a routine method for handling these patients. Severe, progressive exophthalmos, a complication of Graves' disease, recently has attracted the interest of several groups of workers who believe that its presence considerably alters the immediate and subsequent treatment of the disease.

Since the first association of exophthalmos by Parry,<sup>1</sup> Graves<sup>2</sup> and Basedow<sup>3</sup> with the syndrome of hyperthyroidism, the ocular signs have been considered one of the three cardinal features of Graves' disease. These early writers distinguished stare from true exophthalmos but did not explain the mechanism by which proptosis was produced. Naffziger,<sup>4</sup> Ginsburg,<sup>5</sup> Brain and Turnbull<sup>6</sup> and Soley<sup>7</sup> have reviewed the work leading to our present knowledge of the orbital changes that cause exophthalmos. Most workers agree with Naffziger<sup>4</sup> that an increase in the volume of the posterior orbital tissues is responsible for the proptosis, the major change occurs in the extraocular muscles, which show marked edema, destruction of muscle fibers with loss of the usual architecture, increase in fibroblasts and round cell infiltration. The fact that these changes may be minimal or extensive explains the varying degrees of exophthalmos in Graves' disease reported by Cattell,<sup>8</sup> Plummer and Wilder,<sup>9</sup> Mainini,<sup>10</sup> Soley<sup>7</sup> and others.

Severe, progressive exophthalmos has been noted most often after treatment of the hyperthyroidism, although Soley<sup>11</sup> has shown that severe degrees of exophthalmos occur not infrequently during the untreated phase of Graves' disease and may require specific therapeutic

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From the Division of Medicine, University of California Medical School and the Thyroid Clinic, University of California Hospital.

\* Visiting Lecturer from Yale University School of Medicine, Department of Pharmacology.

† Associate Professor of Medicine, University of California Medical School, Associate Visiting Physician and Consulting Pharmacologist, University of California Hospital, Associate Visiting Physician, San Francisco Hospital.





even may show simultaneously evidence both of Graves' disease and incipient myxedema, and present the appearance of a frightened cow with rough skin, protruding eyes, agitation and bovine personality (2) After long-continued Graves' disease with hyperthyroidism the thyroid gland may have suffered exhaustion atrophy (this result frequently led to myxedema in the old days as a sequel to untreated hyperthyroidism) The nervous symptoms and the exophthalmos may persist, however, long after the thyroid has petered out (3) In the idiopathic type, the thyroid gland may not participate in the Graves' disease Why the gland remains aloof we do not understand In some cases it becomes involved after many years of splendid isolation, but in other cases it never becomes involved This type of patient is the most convincing clinical evidence that the thyroid plays only a secondary role in the pathogenesis of Graves' disease

The picture presented above in its simplest terms has described two extremes, namely (a) Graves' disease with marked thyroid activity and (b) Graves' disease with normal or subnormal physiologic activity on the part of the gland In actual fact the entire population of thyroid problems presents a more complex picture All degrees of nervousness and exophthalmos may accompany any degree of metabolic turnover The skilled physician must learn to evaluate the two groups of findings *relative* to each other The dangerous situation is that combination in which the metabolism is low and the exophthalmos great!

#### EXOPHTHALMOS VERSUS LID RETRACTION IN EXOPHTHALMIC GOITER BEFORE AND AFTER THYROIDECTOMY

Stare must be distinguished from true exophthalmos This condition results from retraction of the upper lid which exposes a greater amount of the sclerae and on casual observation gives a false impression of exophthalmos Stare usually disappears after treatment of hyperthyroidism Whereas this satisfies the patient, it should not delude his physician into the belief that the eyes are necessarily less prominent Retraction of the upper lids draws attention to the eyes, while moderate or even severe exophthalmos may escape notice when retraction of the upper lids is absent Retraction of one upper lid frequently causes an illusion of unilateral exophthalmos when in reality the eyes are equally prominent on measurement.

True exophthalmos is recognized easily by determination of the distance from the deepest portion of the lateral wall of the bony orbit to the point of greatest convexity of the cornea and can be measured with a Hertel ophthalmometer The eyes appear uncomfortably prominent and obvious photophobia and excessive lacrimation may accompany the prolonged use of the eyes or the patient's subjective complaint of discomfort in bright light, wind or dust The conjunctivae injected The conjunctivae and sclerae may be edematous to the

point of formation of redundant, sacklike folds that may protrude at the lid margins. Periorbital edema often is present and may involve the eyebrows as well as the lids. Patients frequently complain of frontal headaches and tenderness on pressure against the globes. Impaired convergence indicates weakness of the internal recti muscles. Weakness or complete loss of function of other extraocular muscles also is seen, and in the extreme cases reported by Brain and Turnbull<sup>6</sup> and others there may be complete immobilization of the globes. Weakness of the extraocular muscles may cause the patient to complain of either blurring of vision or diplopia, the muscles involved are determined by careful examination. Increased orbital resistance is demonstrated by making pressure against the eyeballs. If the symptoms and signs still leave reasonable doubt as to the presence of exophthalmos, photographs of the patient taken before the onset of Graves' disease sometimes may be obtained for valuable comparison. These supplement and verify the repeated routine observations with the Hertel ophthalmometer, which are made at each examination of the patient.

In spite of the loss of stare after treatment of hyperthyroidism, approximately 40 per cent of patients with Graves disease will have significant progression of existing exophthalmos which becomes even worse should hypothyroidism occur. In those patients in whom exophthalmos is a presenting symptom of their disease, complications of the exophthalmos must be anticipated, especially when thyrotoxicosis has been treated. After treatment of this disease, progression of exophthalmos may be noted by both patient and physician and is accompanied by an exaggeration of the original symptoms and signs in the eyes. Diplopia may become a constant rather than a transient manifestation of eye fatigue. Orbital and scleral edema increase. Vision may be affected due to papillitis. Finally, corneal ulceration may occur.

#### THE PITUITARY AND ITS THYROTROPIC HORMONE

Schockaert and Foster<sup>13</sup> demonstrated among the first of many investigators that extracts of the anterior lobe of the pituitary produce in ducks, goldfish, guinea pigs and several other species two major responses. These are, first, hypertrophy and *hyperplasia* of the thyroid gland leading to increased liberation of thyroxin into the blood stream under ordinary conditions, and secondly, *pronounced exophthalmos*, which may be accompanied by general edema of the orbital tissues and degeneration of the extraocular muscles.

Furthermore recent experiments with certain drugs containing sulfur have demonstrated that the natural pituitary secretion can lead to a marked increase in thyroid cellular activity. Mackenzie, Mackenzie and McCollum<sup>14</sup> and Astwood<sup>15</sup> have produced extremely hyperplastic thyroids in animals by administering drugs like sulfaguanidine and thiouracil. To a trained pathologist's eye, these tissues are practically

indistinguishable from the primary hyperplasia of severe Graves' disease. Nevertheless, the animals are suffering from severe hypothyroid disease, i.e., lack of thyroxin. In this case, therefore, a marked discrepancy between histological status and actual function occurs.

It can be demonstrated readily that this histological change is due to pituitary activity: first, because examination of the pituitary shows characteristic changes compatible with hypersecretion, and secondly, because if the animal's pituitary be removed, administration of the drugs fails to change the appearance of the gland. There seems to be little doubt, therefore, that the thyroid's activity is under continuous control by the pituitary and that this "thyropituitary axis" is affected by the concentration of circulating thyroid hormone, perhaps through the mediation of some hypothalamic center.

Less is known about the relation of thyrotropic secretion to exophthalmos. It is not clear why an alkaline extract of the anterior lobe should have so specific an influence upon the eyes. Marine<sup>10</sup> has shown that this effect can be produced in the absence of the thyroid. Likewise, it can occur after removal of the upper cervical sympathetic trunk and ganglia. Its action, therefore, appears to be a direct chemical stimulation similar to the effects of estrogens upon the uterine mucosa. It has been shown both *in vitro* and *in vivo* by Seidlin<sup>17</sup> and Rawson<sup>18</sup> that the thyrotropic hormone of the pituitary can be removed from solution by slices of thyroid gland or by the intact thyroid. This is due to a remarkable chemical affinity between the thyrotropic hormone and its "target" gland, namely the thyroid. Presumably the eye becomes involved because the thyroid fails to remove all of the tropic hormone circulating in the blood stream. In addition, if the amount of thyroid tissue is diminished by surgery, the eyes can become more prominent because pituitary secretion probably continues at an increased rate—the so-called "castration phenomenon." In other words, normally the thyroid protects the eyes from thyrotropic hormone by removing it from the blood stream.

This assumption is further supported by the high concentrations of urinary thyrotropic secretion found in cases of Graves' disease (*a*) immediately after subtotal thyroidectomy and (*b*) in the idiopathic cases of exophthalmos. Similarly, high urinary concentrations are found in myxedematous patients in whom the gland has atrophied spontaneously. In brief, then, our present conception of exophthalmos in Graves' disease is that it is due to a chemical effect of the pituitary secretion upon orbital tissues, and that the thyroid tends to protect the eye by sopping up the pituitary substance responsible for the exophthalmos.

This statement must be regarded at present merely as a working hypothesis, but it already has stood successfully the test of repeated applications in clinical cases as well as in experimental animals. The

immediate object lesson of this concept is twofold, namely (1) that to protect the eye one must leave undisturbed the thyroid gland and (2) that one must discourage or inhibit the noxious pituitary activity.

Starr,<sup>19</sup> among others, has demonstrated the inverse relationship between pituitary activity and thyroid activity. Further details concerning this automatic adjustment between thyroid and pituitary activities have been given by Salter<sup>20</sup> in his description of the "thyropituitary axis." From the standpoint of therapy the logical conclusion derived from this concept is that thyrotropic secretion tends to be checked by administration of thyroxin. Indeed, it must be assumed that Graves' disease *in itself* tends to be self-limiting because the greater the hyperthyroidism, the more inhibition will be applied to the pituitary. Perhaps the cyclic exacerbations and remissions characteristic of the disease are due to vacillations of some mechanism resembling a thermostat and located in the lower brain. Although unproved, this concept will afford the basis for further therapeutic approaches to this disease which includes so many psychosomatic aspects.

#### TYPICAL CASES

The following case history illustrates moderately severe exophthalmos in a patient with frank hyperthyroidism.

*Case I. Moderately Severe Exophthalmos Following Subtotal Thyroidectomy*—Mr. B. S. L., a clerk, thirty-two years old, entered the University of California Hospital on Feb. 11, 1941, because of exophthalmos of two months' duration. Essential features of the present illness were easy fatigability and dyspnea with exercise for one month, increased warmth, excess perspiration, diarrhea, nervousness and irritability and a lump in the neck for three to four weeks. His right eye had become more prominent during the two weeks prior to entry.

*Family History.* Not contributory.

*Past History.* He was born in Hawaii and had been in the United States for ten years. He remembered no illness or operations except for a nasal operation in 1926.

On physical examination he appeared to be a hyperkinetic Chinese who was flushed, warm and perspiring. There was bilateral exophthalmos; the right eye was more prominent than the left and showed more periorbital edema. Lid lag was present. His thyroid was enlarged. His heart was overactive with a loud mitral systolic murmur. The pulse rate was 110, blood pressure, 120 systolic and 78 diastolic. He had a fine tremor of his extended fingers. The basal metabolic rate was +38 per cent. Blood count and urine examinations were normal. Chest film was normal except for enlargement of thyroid and cardiac shadows. An electrocardiogram was normal except for sinus tachycardia. His eyes measured 17 mm. on the right and 16 mm. on the left (Fig. 42).

After the usual preoperative preparation a subtotal thyroidectomy was done on March 6, 1941, and 28.5 gm. of hyperplastic thyroid tissue were removed leaving about 60 gm. in situ. His postoperative course was uncomplicated. He gained from 131½ pounds at entry to 151½ pounds in May 1941. His basal metabolic rate was -4 per cent and plasma cholesterol was 157 mg. per cent. His eyes showed more exophthalmos, edema and diplopia and measured 21 mm. on the right and

18.5 mm on the left. He was given Armour's thyroid, and was maintained on 0.1 gm and two drops of Lugol's solution daily

By July 1941, the patient's weight had decreased to 146 pounds, diplopia was less noticeable to the patient, and his eyes measured 20.5 mm on the right and 19.5

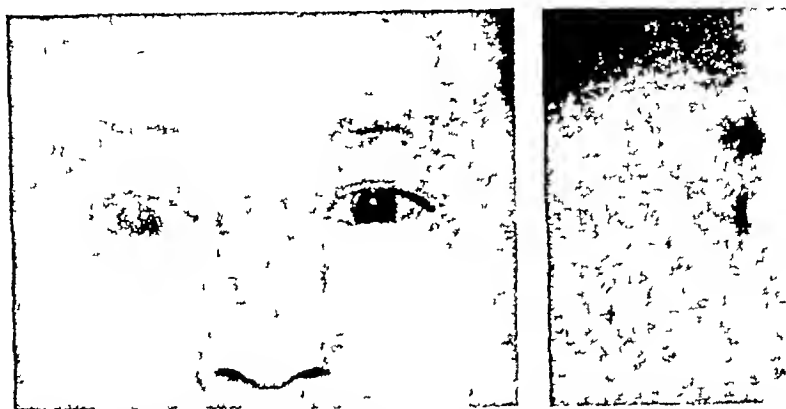


Fig 42—Photographs of patient B S L during phase of hyperthyroidism. At the time these pictures were taken his right eye measured 17 mm and his left eye 16 mm.

mm on the left (Fig 43). On the same regimen, by August 25, 1941, his right eye measured 20.5 mm and his left eye 21 mm. Re-examination in the hospital was carried out and no important information was added, his metabolic rate was -1 per cent and plasma cholesterol 163 mg per 100 cc. By January 1942, his right

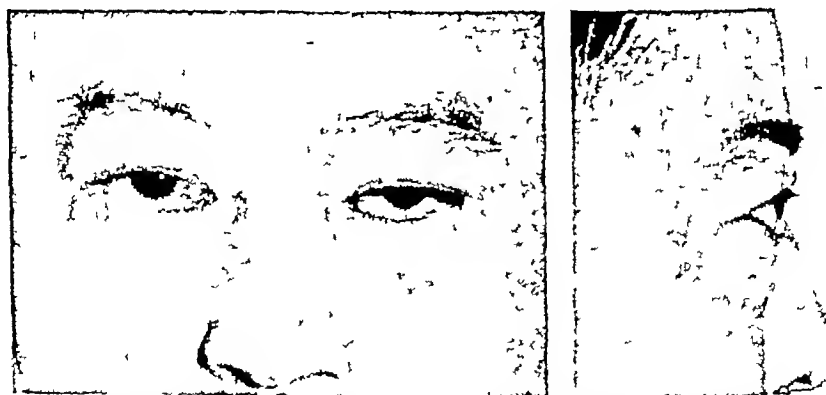


Fig 43—Photographs of B S L fifteen months after subtotal thyroidectomy. His right eye measured 20.5 mm and his left eye 20.5 mm.

eye measured a little less than 20 mm and his left 20.5 mm and on August 3, 1943, his right eye measured 19+ mm and his left eye 20— mm. His eyes were much better at this visit with only slight diplopia on looking to the extremes of right and left.

As an example of a fulminating case, the following short history is given

**CASE II—Severe Exophthalmos Following Subtotal Thyroidectomy**—A forty-two-year-old male married merchant consulted his physician because of nervousness. For nearly a year his eyes had been increasing in prominence so that his friends remarked about them. There had been some tendency toward tachycardia on excitement but the pulse had been found to be slow when the patient was at ease. There had been slight gain in weight during this period despite poor appetite. The patient had not minded the heat and had suffered from cold. There had been only mild sweating even in warm weather. The basal metabolic rate was found to be between +19 per cent and +14 per cent.

Examination revealed only questionable enlargement of the thyroid together with moderate exophthalmos and fine tremor of the hands. After consultation with an internist the thyroid was removed subtotally.

Within three days both eyes became markedly prominent. The sclerae became erythematous. Within a week this patient was unable to shut his swollen eyelids and marked periorbital edema was present. Purulent exudate accumulated in both eyes from which positive pneumococcus cultures were obtained. Corneal ulceration, bilateral, was demonstrated with fluorescein. An attempt to suture the lids together failed.

Ten days after the operation the everted angry red conjunctival sacs of both eyes were flush with the skin and were mistaken for mercurochrome dressings at first sight. In the center of each was a dirty spot which represented the remains of the crumpled cornea. It was impossible to distinguish between sclerae and conjunctival mucosa. The small venules about the eyelids were distended and the skin so edematous that the characteristic retrocession of the eye was obliterated. The aqueous humor had escaped on both sides and the patient was completely blind. The blood hormonal iodine taken at this time was 81 micrograms<sup>21</sup> per cent, i.e., just over the upper limit of normal (80).

We are indebted to Dr. Louis P. Hastings of Hartford, Connecticut for the following *pathological report*:

**Grossscopic.** Specimen received in formalin consists of masses of recognizable thyroid tissue marked by multiple incisions. Reconstruction does not allow accurate measurement but the total weight of tissue is 30 gm and the contour suggests a moderate enlargement of the thyroid gland. The fixed parenchyma is yellowish in color somewhat firm without grossly visible colloid.

**Microscopic.** Multiple sections are similar showing a diffuse but varied picture. The variations run from normal thyroid parenchyma to scattered small islands of typical though mild, hyperplasia to other areas which represent typical involution. There are scattered nodules of lymphoid tissue and several areas in which the connective tissue trabeculae are thickened. The entire picture appears consistent with a moderately hyperplastic thyroid which is undergoing and has undergone involution.

**Pathological Diagnosis.** Parenchymatous Hyperplasia with Involution.

This fulminating course was obviously a rather unusual one, but entirely characteristic. The eye signs, at first only moderate in extent, immediately after operation became very severe. It should be noticed that although the nervous group of symptoms brought this man to a doctor, there was very little evidence of true hyperthyroidism as shown by increased caloric consumption. Indeed the patient had gained weight and suffered from cold. These facts are warning signals in cases of this sort. Why remove the thyroid if it is not hyperactive?

## PATHOLOGICAL FINDINGS IN BIOPSIED OR AUTOPSIED CASES

Two factors influence the course of exophthalmos. Because the orbit is for practical purposes a closed space, an increase in the orbital contents necessarily results in a forward and probable downward displacement of the eyeball. If the orbit is large, obviously more space is available within it and edema of the orbital contents produces less effect than in an orbit of smaller dimensions. Venous return is more apt to be impaired within orbits of small volume. This impairment may be accompanied by rapid progression of exophthalmos with functional disturbances of the extraocular muscles, corneal ulceration, papillitis and panophthalmitis.

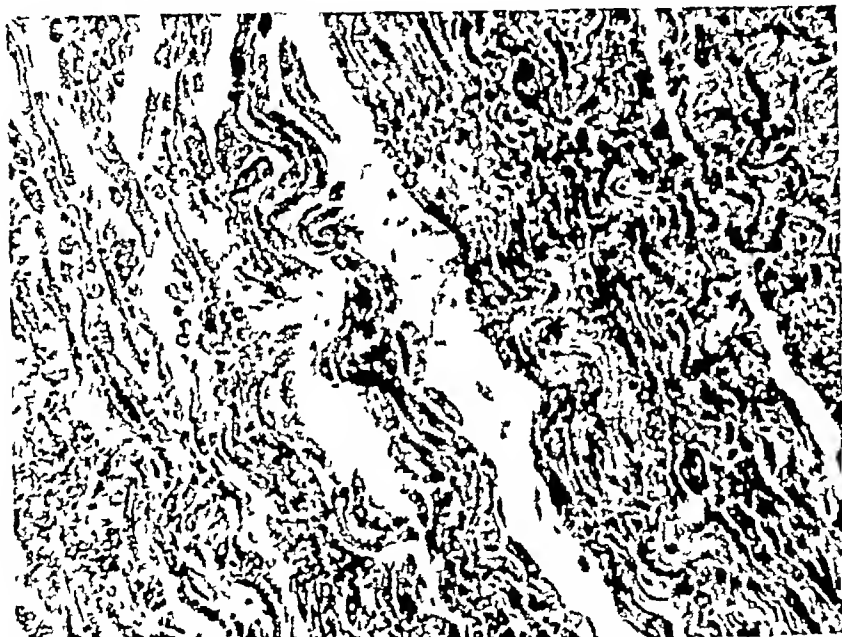


Fig. 44—Photomicrograph of a section of the superior rectus muscle taken during supraorbital decompression in a patient with hyperthyroidism, severe exophthalmos and bilateral corneal ulceration ( $\times 300$ )

The second factor is the degree of inflammatory reaction in the extraocular muscles (Fig. 44) and orbital fat. In most instances, the extraocular muscles obtained at biopsy during orbital decompression or at postmortem show evident edema. Occasionally, cases such as those having supraorbital decompression as determined by Dr. Howard C. Naffziger, or members of his staff, show relatively little edema. However, pathological techniques generally employed do not permit an accurate estimate of edema that can cause an increase of even 10 per cent or more in the size of extraocular muscles. Usually other changes such as degeneration of muscle fibers, infiltration with round cells,



especially about blood vessels and fibrosis are seen in microscopic sections. Certainly muscles seen grossly during orbital decompression are pale and several times normal size. Orbital fat varies considerably in amount among individuals, but if much fat is present in the posterior orbit, edema of this tissue may play an important part in ocular proptosis. Biopsy of orbital fat can be associated with bleeding that is difficult to control, consequently it is not often done. Only patients with orbits of large capacity that contain small amounts of fat should risk having severe exophthalmos with their Graves' disease.

### THE EFFECT OF THYROID THERAPY

If the role of the pituitary in controlling thyroid activity really is regulated by the concentration of circulating thyroid hormone, it should follow logically that thyroid activity can be suppressed by increasing the concentration of thyroxin in the blood stream. Presumably this sort of automatic suppression occurs in hyperthyroidism just as it occurs in the normal individual, with the exception that in Graves disease the automatic shut-off mechanism is set at too high a point. Nevertheless, just as the malarial chill and rigor can be shortened by raising the patient's body temperature so that he becomes feverish sooner, so by increasing the patient's hyperthyroidism it should be possible to cut off the pituitary trophic activity.<sup>22</sup> Obviously such a measure constitutes heroic therapy, because actually it is adding insult to injury as far as hyperthyroidism is concerned. Such heroic therapy, however, may occasionally be justified if vision is at stake.

When this approach is undertaken it must be done under ideal conditions. The patient must be hospitalized and kept at complete rest. Due care must be taken to maintain nutrition and especially the reserves of liver glycogen despite the increased caloric consumption. Due consideration of the risk to the patient's cardiac reserve must be paid. All such hazards must be weighed carefully by the attending physician in deciding how far thyroid therapy may be pushed. The following brief case history will illustrate the procedure.

CASE III—A thirty six year-old single male janitor complained of bilateral exophthalmos of seven months' duration. Both eyes showed marked chemosis and conjunctivitis with exudate. The lower lids contained 3 mm nodules which, on biopsy, consisted of chronic inflammatory cells of the lymphoid and eosinophilic granulocyte series. There was no change in appetite nor loss of weight. The thyroid was not palpable and the skin was normal. Tremor and tachycardia were absent. The basal metabolic rate was -10 per cent. The Ludde exophthalmometer showed the cornea of each eye to be 24 mm anterior to the lateral orbital bone margins. The concentration of circulating protein-bound iodine was normal, i. e., 6.4 micrograms per cent.

In view of the patient's good physical condition and negative heart examina-

tion, he was adjudged a suitable risk for increased thyroid activity. Accordingly, thyroxin therapy was given for five days, 1 mg intravenously each day. This series of injections increased the circulating protein-bound iodine to 103 micrograms per cent but the basal metabolic rate, as calculated, rose only slightly. Thereupon four more daily injections of 1 mg of thyroxin intravenously were given. At this time the recorded basal metabolic rate was  $-8$  per cent. The patient's general condition was good but his eyes were unchanged. Accordingly more heroic therapy was undertaken after due deliberation.

On the first day 10 mg of thyroxin were injected intravenously. Because late in the second day the patient's beginning response (mild fever, muscle pains) was slight, another 10 mg intravenously were given after due deliberation. Thereafter for five days heavy sedation with barbiturates was given. At the end of this time the basal metabolic rate was  $+34$ , and the circulating hormonal iodine was 18 micrograms per cent. The conjunctivitis and periorbital edema had begun to subside.

A week later measurement of both eyes gave the values for corneal prominence as 18 mm (right eye) and 17.5 mm (left eye). By this time the nodules in the eyelids had all but disappeared and only one eye remained bloodshot. Thyroid therapy by mouth (10 grains a day) was instituted and slowly tapered off to 3 grains a day over the course of a month. The patient continued to improve remarkably, and within three months appeared normal except for moderately prominent eyes. He still had to be careful, however, not to get ashes in his eyes because of the susceptibility to irritation.

The patient continued at his job, leading a quiet secluded life and avoiding excitement, until summoned by Selective Service. He had been cautioned that undue excitement would probably cause his disease to recur. This prediction was verified after a few weeks of "hardening" at an army camp.

It must be emphasized that this approach is heroic although logical. It must be undertaken only under ideal circumstances and under skilled advice.

The risk of cardiac disability must be considered constantly and weighed against loss of vision. Absolute quiet and heavy sedation should be maintained. Successive measurements of the prominence of the eyeball should accompany repeated measurements of basal metabolic rate and of circulating protein-bound iodine. More experience is needed before the overall value of this procedure can be assessed. Obviously, it is better suited to younger vigorous individuals.

#### MANAGEMENT OF PATIENTS TREATMENT OF EYES INCLUDING INDICATIONS FOR SUPRAORBITAL DECOMPRESSION

The patient with severe exophthalmos and hyperthyroidism should be treated in such a way as to protect him, if possible, from further proptosis. If his thyroid is not too large (not over 50 gm) as estimated by examination and his hyperthyroidism not critical, *x-ray therapy* to the thyroid may be instituted. This method of subtotal destruction of the thyroid is a gradual one and hypothyroidism is a rare complication. The usual method is to give three courses of 900 roentgens each with six weeks between courses, the individual course consists of 150 roentgens on each of six successive days.

When the hyperthyroidism is severe and the thyroid large or nodular, *subtotal thyroidectomy* is preferred during which more thyroid tissue (5 to 8 gm) than usual is left in situ. Hypothyroidism must be watched carefully and treated early when it occurs. With either form of treatment, the patient should be kept under close observation and urged to return for care should his eyes bother him in any unusual way.

Treatment of the eyes per se involves protection from dust and irritation. Glasses with side pieces may be recommended. If there is blurring or diplopia the patient should be fitted with prism lenses. Sterile isotonic saline solutions may prove soothing. Five per cent sulfathiazole ointment may be used if there is corneal ulceration, although some patients complain of discomfort from its use. The lids may be sutured for cosmetic reasons so that less sclera is exposed or for protection of the eyes during the administration of a general anesthetic. We have seen one patient (see Case I) who had entropion that was temporarily relieved by the use of a strip of adhesive tape placed just below the lower lid margin and fastened down over his cheek so that the lower lid was everted.

In spite of a rather extensive experience at the University of California Hospital, there is no unanimity of opinion as to the indications for *supraorbital decompression*. Failing vision from papillitis and perhaps secondary optic atrophy necessitate operative intervention. Exophthalmos of such a degree that the eyes are partly open during sleep may allow drying, abrasion and ulceration of the cornea and this situation often is an indication for decompression. Extreme edema of the sclerae and conjunctivae may persist, as happened in one of our patients when decompression is postponed too long. On the other hand, a patient like that one whose history is related (Case I) may begin to have measurable recession of his eyes at a time when both attending physicians and neurosurgical consultants have decided that decompression is indicated. Only repeated examinations of a given patient and the help of the neurosurgeon will permit arrival at an adequate decision.

Supraorbital decompression as described by Naffziger is carried out through a right or left frontal approach. The dura is elevated from the orbital plate and the orbital roof is removed as widely as possible including the roof of the optic foramen in some instances. During the first three postoperative days temporary accentuation of orbital edema may obscure partially the regression of exophthalmos but later the exophthalmos may decrease 6 to 9 mm by measurement. In a few cases, there may be little or no regression. Pulsation of the globe occurs to some degree after decompression and as reported by Ginsburg,<sup>5</sup> may be uncomfortable for the patient.

## COMMENT AND SUMMARY

Physicians and surgeons alike have come to regard with apprehension cases of Graves' disease with severe exophthalmos.<sup>12 23</sup> The actual exophthalmos must be distinguished from exposure of the eyeball due to simple retraction of the upper lid.<sup>7</sup> The degree of exophthalmos can best be measured with suitable exophthalmometers resting against the lateral bony orbital margins. Even so, the evaluation of such measurements, as regards prognostic and therapeutic interpretation, depends upon certain factors, notably the shallowness of the bony orbit and its general configuration. Prolonged and progressive exophthalmos of this type leads ultimately to varicosity of the orbital veins with ensuing ecchymosis of the conjunctival sacs and marked periorbital edema. Despite local antisepsis, including sulfonamides, infection of the eye may occur and lead to corneal ulceration, loss of aqueous humor, prolapse of the iris, and ultimately panophthalmitis. One eye may be affected more than the other, and occasionally one eye may increase in prominence as the other recedes. During this process edema and degeneration of the extraocular muscles lead to partial paralysis of ocular movements (ophthalmoplegia).

Simple local measures such as antisepsis, douching and even suture of the lids are often ineffective in preventing dissolution of the visual apparatus. In cases of doubt, the experienced physician will resort to the heroic measure of orbital decompression by surgical removal of portions of the bony orbit. Before this stage is reached, however, thoughtful medical management should be instituted in the hope of avoiding a desperate situation.

In the first place, surgical removal of thyroid tissue should be avoided in those cases in which the patient, although very nervous and exophthalmic, shows little evidence of heightened metabolism. In the second place, especially in the younger vigorous individuals, the risk of producing artificially a state of marked hyperthyroidism should be weighed carefully against the anticipated inhibition of pituitary secretion with relief of eye symptoms. In so doing, general supportive measures must not be neglected. These include complete rest with sedation to protect the circulation, maintenance of nutrition with emphasis upon fluid, vitamins and carbohydrate, the judicious use of eye salves and lotions, and the protection of the eyes from external irritation or contamination by dressings and other devices so designed as not to interfere with free drainage.

On the whole, prevention and foresightedness should be the watchword in treating these cases. The physician who handles thyroid problems must bear in mind constantly the possibility of this complication. Likewise, the surgeon who specializes in thyroid operations must endeavor to sift out this minority in the preoperative population, lest he add to their temporary distress a permanent and ghastly affliction.

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# DIABETES MELLITUS AND PULMONARY TUBERCULOSIS

JOHN A. FOLEY, M.D., F.A.C.P.\*

AND

JOHN B. ANDOSCA, M.D., F.C.C.P.†

## INCIDENCE OF TUBERCULOSIS IN DIABETES

THE frequent combination of diabetes mellitus and pulmonary tuberculosis is an accepted fact of clinical medicine. In 1883 Windle<sup>9</sup> reported that out of 333 diabetic cases which came to autopsy 50 per cent had active tuberculous lesions, in 1906 Nannyn<sup>5</sup> found the two diseases associated in 41 per cent of cases at postmortem examination. In 1931 Banzai<sup>1</sup> concluded from a study of the available literature that tuberculous disease was three times as common among diabetics as among the general population. Root<sup>6</sup> in 1934, after investigating the incidence of tuberculosis morbidity among 1651 diabetic patients, also confirmed Banzai's conclusions that the incidence of tuberculosis was three times as common among diabetic as among the general populace.

## REASONS FOR THIS FREQUENCY

The exact cause of the high incidence of tuberculosis among diabetics has not been entirely explained. Steinbaek<sup>7</sup> and his co-workers have furnished some experimental evidence. They found that pan-creatomized diabetic dogs were less resistant to a known dose of tubercle bacilli than a control group of healthy animals. This suggests that the increased susceptibility to tuberculosis of the diabetic dogs may be due to faulty carbohydrate metabolism.

Authorities maintain that, in spite of the decline in mortality rates from tuberculosis, the mortality from tuberculosis among diabetics is steadily increasing. It has been definitely shown that patients with poorly controlled diabetes are much more prone to develop pulmonary tuberculosis than those whose disease is well controlled. Himsworth<sup>3</sup> showed that, in a series of 300 diabetics whose disease was well controlled, only two developed pulmonary tuberculosis.

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Chief-of Staff, Boston Sanatorium. Clinical Professor of Medicine, Boston University School of Medicine. Director Fifth and Sixth Medical Services, Boston City Hospital.

† Chief Resident Physician, Boston Sanatorium. Instructor in Medicine, Boston University School of Medicine.

## CLINICAL FEATURES

It is generally agreed that pulmonary tuberculosis in the diabetic usually appears suddenly and progresses quite rapidly. Such a sudden appearance of the tuberculous lesion can only be explained in one of two ways. Either the diabetic is unusually vulnerable to tuberculous infection, or the tuberculous lesion lies deep-seated in the lung and remains undetected until it rises to the surface and produces its physical signs. It is our opinion that the latter explanation, namely, the deep-seatedness of the tuberculous lesion in the diabetic, accounts for the sudden appearance of the disease as soon as it reaches the surface of the lung.

Consequently we recommend radiological examination of every diabetic's chest every six months. Clinicians report quite a discrepancy between radiological and clinical examination in diagnosing tuberculosis in the diabetic. Himsworth<sup>8</sup> states that in his clinic, out of a series of 230 consecutive diabetic patients, pulmonary tuberculosis was detected by clinical means in two and suspected on clinical grounds in two others. In this same series radiological examination revealed a lesion in the lung in fifteen cases. Thus by clinical methods tuberculosis would have been detected in only 1.4 per cent of the patients, although it was actually present in 6.5 per cent.

The pulmonary tuberculosis found in the diabetic does not show any remarkable characteristic clinical symptoms or physical signs. Errors of course, are often made in ascribing these symptoms to the patient's diabetes rather than to his tuberculosis. A striking feature that was noted in the course of the diabetes in the adult was *rapid loss of weight* preceding the development of tuberculosis. Some patients have lost as much as 75 pounds in several months.

As regards the *roentgenographic examination* we have sometimes noticed the so-called tubercular-diabetic or the butterfly type of lesion. The salient features of this type may be described as a soft exudative process spreading from the region of the hilum toward the periphery most commonly in the midzone of the lung, leaving the apex and at times the extreme base free from disease.

It is the consensus that in the great majority of cases diabetes does not follow the tuberculous infection but rather tuberculosis afflicts the diabetic.

In our series of twenty-eight cases, diabetes definitely preceded the tuberculous infection in twenty-two, tuberculosis preceded the diabetes in two cases, in three cases the diagnosis of pulmonary tuberculosis and diabetes was made at the same time and we were in no position to say which condition came first.

The *age distribution* of the tuberculous diabetic patient parallels that of diabetes rather than that of tuberculosis in the general popu-



lation (Table 1) The average age in our series was forty-seven years. The oldest patient was sixty-seven and the youngest was twenty-one. The group comprised sixteen male and twelve female patients, all were of the white race except three, two of whom were colored and one Chinese.

TABLE 1—ANALYSIS OF DATA ON 28 CASES OF DIABETES AND PULMONARY TUBERCULOSIS

Patient No.	Age	Sex	Race	Diagnosis Diabetes	Diagnosis Tuberculosis	Classification of Tuberculosis	Blood Sugar at Beginning of Treatment	Average Blood Sugar at Present	Weight at Beginning of Treatment	Last Weight	Results and Comments
1	41	M	W	1/34	8/16	Mod. adv.	563	150	183	191	In sanatorium. Pnx. L.
2	47	F	W	1/33	9/40	Far. adv.	645	170	160	184	In sanatorium
3	60	M	W	5/41	5/42	Mod. adv.	197	115	158	185	In sanatorium
4	24	M	W	2/35	2/43	Far. adv.	167	128	137	145	In sanatorium
5	54	M	W	2/31	2/23	" "	230	180	137	140	In sanatorium Pnx. L.
6	58	M	N	4/28	10/32	" "	166	130	160	184	In sanatorium
7	41	F	W	6/42	1/43	" "	312	200	129	115	In sanatorium
8	41	F	W	3/41	10/42	" "	276	200	100	105	In sanatorium
9	59	F	W	6/40	4/41	" "	260	150	105	151	In sanatorium
10	57	M	W	2/30	4/42	" "	294	175	109	130	In sanatorium
11	58	F	W	8/32	9/42	Mod. adv.	170	150	101	116	In sanatorium Phrenic R.
11	24	M	W	4/30	5/42	Far. adv.	266	200	135	154	In sanatorium
11	21	M	W	10/34	8/39	Mod. adv.	154	135	120	136	In sanatorium Pnx. R.
14	48	M	W	4/45	4/45	Mod. adv.	170	140	105	124	In sanatorium
15	59	M	W	7/31	7/41	Far. adv.	140	150	115	130	Dead
16	56	M	Y	4/40	2/42	" "	220	135	125	120	Dead
17	43	M	W	8/40	9/41	" "	210	140	120	119	Dead
18	44	F	W	10/40	9/41	" "	185	110	110	112	Dead
19	67	M	W	9/41	4/42	" "	192	115	119	110	Dead. Autopsy also showed bronchogenic carcinoma.
20	37	F	N	6/38	8/41	" "	166	100	162	130	Dead. Pulmonary hemorrhage
21	48	F	W	6/40	10/41	" "	298	190	125	129	Dead
22	51	F	W	1/41	1/41	" "	245	115	100	100	Dead
23	21	F	W	10/30	10/42	Mod. adv.	151	90	102	110	Discharged Pnx. R. and Lysol
24	39	M	W	3/41	3/41	" "	190	100	85	115	Discharged
25	31	F	W	1/39	1/49	" "	143	110	90	113	Discharged. Pnx. R.
26	44	F	W	1/35	12/36	" "	225	200	165	194	Discharged. Pnx. L. and Lysol
27	56	M	W	5/15	5/10	" "	165	110	170	130	Discharged
28	37	M	W	1/17	3/42	" "	211	130	129	138	Discharged. Pnx. L. and Lysol

<sup>1</sup> Pneumothorax.

<sup>2</sup> Pneumocystis.

The tuberculosis which is associated with diabetes is in the great majority of cases of the far advanced type. The stage of the pulmonary disease in the entire group of twenty-eight cases classified according to the criteria adopted by the National Tuberculosis Association was as follows: minimal stage, none, moderately advanced 11, or 39 per cent, far advanced, 17, or 61 per cent (Table 2). It is in

TABLE 2—STAGE OF PULMONARY TUBERCULOSIS

	Number	Per Cent
Minimal	0	0
Moderately advanced	11	39
Far advanced	17	61

teresting to note that no case in the series could be classified as minimal. All the patients in the series had a positive sputum. We recommend sanatorium care for all diabetics with a tuberculous lesion until both conditions are stabilized and controlled.

#### TREATMENT OF THE COMBINED DISEASES

For the past two years it has been our policy to treat our tuberculous diabetics on a high caloric house diet of at least 3000 calories. The three main component foodstuffs are roughly in the proportion of carbohydrate 3, protein 1 and fat 1, in addition to sufficient minerals and vitamins. An example of an ordinary daily diet consists of 345 gm of carbohydrates, 120 gm of protein and 130 gm of fat, totalling about 3030 calories. This procedure has been successfully employed by Kutschera-Aichbergen<sup>4</sup> (1931) and by Vrhovae<sup>8</sup> (1937).

Fishberg<sup>2</sup> (1932) stated that patients submitted to a low caloric diet certainly lose their glycosuria but at the same time a rapid progress of the pulmonary tuberculosis occurs. Again, if the limitation of calories in a diabetic helps to decrease the patient's resistance to pulmonary tuberculosis, we believe that the opposite, namely, a high caloric intake, should be beneficial to a diabetic patient with tuberculosis. It was special attention to these points which led us to stress the importance of a high caloric diet supplemented by ample minerals and vitamins.

We do not advocate a high caloric diet for the tuberculous diabetic patient without strict control of his diabetes through the use of insulin. The diabetes should be brought under control as soon as possible so as to retard any further spread of the tuberculous lesion. To this end no attempt is made to build up the patient's diet from one of low to one of high caloric value, nor is any attempt made to spare the amount of insulin required to bring about control. The full high caloric diet is given as soon as the patient is admitted to the sanatorium. Fasting blood sugars in the beginning are taken weekly and later every two weeks. Our patients are given their required dose of protamine zinc insulin and a small dose of regular insulin every morning before breakfast. The practical advantage of protamine zinc insulin in treating tuberculous diabetics is its reduction of the frequency of injections. Furthermore, by its use it is possible to have a steady and constant formation of glycogen and in addition the danger of severe insulin reactions is definitely reduced.

Examinations of the urine are made on the wards daily before each meal and depending on the color reactions the following dosages of regular insulin are given: (a) green reaction, 5 units, (b) yellow reaction, 10 units, (c) olive reaction, 15 units, (d) orange reaction, 20 units. In addition, every morning urine specimen is examined for

sugar and ketone bodies by the laboratory technicians. The criteria of satisfactory control should be a urine consistently free from ketone bodies and either free of sugar or containing the smallest amount of sugar that the patient can tolerate without experiencing symptoms. We find that in the older cases a moderate hyperglycemia is harmless and excessive means to lower it are not employed.

Occasionally we find that in cases with much toxemia the patient may be unable to ingest a high caloric diet made up of so much solid food. In that case a fluid or semifluid diet is devised containing the full amount of carbohydrate, protein and fat. Later as the condition improves this diet can be slowly changed to contain the more solid foods. The same general principles that are followed in the treatment of the nondiabetic tuberculous patient are advocated for the tuberculous diabetic patient. Fresh air, rest and lack of worry are all essential. Some form of collapse therapy such as pneumothorax, phrenic nerve surgery, or thoracoplasty where indicated should be carried out.

Of course, due to the age and coexisting cardiovascular changes in many of the patients collapse therapy is definitely limited. The entire group was submitted to basal metabolic rate and electrocardiographic studies but no remarkable conclusions were derived except that patients with very active tuberculosis tended to have higher basal metabolic rate readings.

#### RESULTS OF TREATMENT

The results after two years of nutritional studies have for the most part been very encouraging. Practically every patient showed a weight gain and a definite improvement in his sugar tolerance. It was noted that the average weight gain in the eleven cases classed as moderately advanced was 26 pounds while the average weight gain in the seven far advanced cases was 5 pounds. The sputum became negative for tubercle bacilli in thirteen cases (47 per cent).

Out of the group of twenty-eight patients fourteen are still in the sanatorium and doing well, eight are dead and six have been discharged (Table 3). It is interesting to observe that all the patients

TABLE 3—PRESENT STATUS OF PATIENTS

	Number	Per Cent
In Sanatorium	14	50
Dead	8	28
Discharged	6	22

who died had far advanced tuberculosis while those who were discharged had moderately advanced disease. In one case which came to

autopsy the patient was found to have a bronchogenic carcinoma in addition to diabetes and pulmonary tuberculosis

### CONCLUSIONS

At one time the combination of diabetes and pulmonary tuberculosis was considered fatal. The advent of insulin has certainly altered this prognosis. It is interesting to note that the tuberculosis death rate among diabetics per 1000 fell from 11 prior to the use of insulin to 4 after the use of insulin.

It is safe to say that in the sanatorium a well-controlled diabetic with tuberculosis is no more difficult to treat than a person suffering from tuberculosis alone. Early diagnosis of the tuberculous infection is the all-important factor, for, once tuberculosis has reached an advanced stage, the prognosis is poor even when the diabetes is controlled. The surest and quickest method of detecting pulmonary tuberculosis in the diabetic is by routine radiological examination of the chest every six months.

At the present time, earlier diagnosis, proper use of the high caloric diet, insulin administration and collapse therapy have all contributed in prolonging the life of the tubercular diabetic.

### SUMMARY

- 1 A two-year nutritional study of twenty-eight patients with co-existing diabetes and pulmonary tuberculosis was made.
- 2 The composition of the average diet for the entire group yielded at least 3000 calories. The three main foods were roughly in the proportion of carbohydrate 3, protein 1 and fat 1.
- 3 The diabetes was controlled as soon as possible by the use of protamine zinc insulin and regular insulin.
- 4 Frequent blood sugar estimation and urine examinations are essential.
- 5 The pulmonary tuberculosis was classified as moderately advanced in eleven and as far advanced in seventeen patients. No case could be classified as minimal.
- 6 The average age in the twenty-eight cases being forty-seven years, collapse therapy was somewhat limited.
- 7 A weight gain and improvement in sugar tolerance were observed in a great number of the patients.
- 8 Of the twenty-eight patients, fourteen are still in the sanatorium and doing well, eight are dead and six have been discharged.
- 9 A poor prognosis is invariably given in the case of a diabetic with far advanced tuberculosis even if the diabetes is controlled.
- 10 The importance of early diagnosis of the tuberculous lesion, a high caloric diet and careful control of the diabetes cannot be over-emphasized.

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## THE TREATMENT OF GONORRHEA UNDER EXISTING CONDITIONS

P S PELOUZE, M D \*

So far as the therapy of gonococcal infections is concerned, history has been so busy repeating itself that no sooner did we awaken from one dream state than we were plunged into another seemingly more beautiful. For years out of mind this was a regular experience for the medical profession. The "new treatment" only had to be more easily carried out than the last one to gather its followers who stayed on the merry-go-round grasping for the brass-ring until it slowly disappeared that, so far as results were concerned, the brass-rings were all pretty much alike. Of course, if one ring had a little more of the bizarre to it than its predecessors more physicians made a grab for it and, seemingly, they cherished it longer.

Thus, methods of treatment that had real things to offer frequently were thrown aside because they were "just too much trouble," they were used so poorly that their results were not impressive. Little time was spent in studying the disease itself and, as often as not, treatment was carried out on an I-hope-for-a-miracle basis when there were no miracles to be had.

All of this was bad enough when the physician alone held the therapeutic reins for those who consulted him, and his sole sources of information were the medical meeting, the medical press and his own clinical observations. But when the age of gonorrhea miracles did come along and the lay press became courageous enough to mention the name of the disease, the physician no longer was head-man in the picture. Patients rarely asked for information from him—they gave it. There was ushered in the era of tablet-worship and, more often than not, the physician, in those places where the druggist did not take over, became merely the dispensers of the miracle-tablets.

### TODAY'S MIRACLE "CURES"

**Sulfathiazole**—It got noised around that 80 per cent of the gonococcal infections could be cured in five days by the use of sulfathiazole. It even was said in the *Readers Digest* that, with a bit of cooking, 99 per cent of the patients could be quickly and safely cured. Doctors believed the first and the laity credited the second just because the medical interpreter Mr. De Kruiff said it. Then, time and a world disappointment showed the medical profession that the first was

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\* Assistant Professor of Urology, University of Pennsylvania, Special Consultant, U S Public Health Service

so, just as they have shown many a saddened lay victim that Mr De Kruiff could be in error at times and that this was one of the times

**Penicillin**—Now penicillin has entered the picture of gonorrheal therapy and introduced a super-miracle age which beyond question could be the answer to the prayers of both the maiden and her boy friend. There is at present every reason to believe that under proper dosage one course of penicillin treatment will cure around 97 per cent of the patients and that a repeat course of perhaps higher dosage usually will cure the few failures on the first. Science truly has mastered the disease but—and it is rather a large *but*. There is too much gonorrhea for the too little penicillin and the wonder-drug is good for so many things beside gonorrhea—diseases that carry mortality rates—that there will have to be far more than there now is for the poor old gonorrheic to get much of it after it is proved so good for him.

Also, the present administration of penicillin is a matter of intravenous or intramuscular injection at two or three-hour intervals for twenty-four hours or more. So it is a hospital procedure that hardly lends itself to either office or clinic practice. It is going to take many beds to treat all gonorrheal patients with penicillin.

The general availability of penicillin apparently is rather well removed from the present, and even were it to become quickly available commercially it is probable that few gonorrheics could pay its cost or that few health agencies could or would pay it for them. Until all of these things are cared for we shall have to confine ourselves largely to being deeply thrilled over what science has accomplished and then get realistic and make the best use we can of the other things.

**Pyrotherapy**—Immediately pyrotherapy comes to mind. It, too, has been lauded almost to the sky as a means of curing our sulfonamide failures. Unquestionably it is a great addition to our curative efforts even if it is not quite so effective as generally used, as we have been led to believe. One is safe in saying that properly used it will cure or promote cure in by far the large majority of those whom sulfonamides do not cure. Its lack of availability in almost all small cities and towns and even in some of the larger ones puts it beyond the physical and, probably, financial reach of at least 90 per cent of the gonorrheics in civilian circles. So for a long time to come most physicians and their patients will have to view it from a distance.

#### A PRACTICAL APPROACH IS NEEDED

Thus, after rather a long dissertation and some unfortunate eliminations we, at last, have arrived at the physician's office and the usual clinic and just how they can handle the problem with today's armamentarium until tomorrow makes more generally available those other things. There will be a lot of gonorrhea to treat in that rather uncertain meantime, and it will not be cured by the dreams of better days.

to come. It will be cured because we intelligently use the things we have at hand and make ourselves mean more in the general picture than just the means by which our patients can get their sulfonamide tablets. And we will do a far better job at it if we start by gaining a better knowledge of the underlying principles of gonococcal infections than now is generally held.

#### SULFONAMIDE-PRODUCED ASYMPTOMATIC STATES VERSUS CURE

Before going into treatment methods it is of extreme importance that we realize that there is an unfortunate difference between sulfonamide-produced asymptomatic states and real *cure* and that difference can rather safely be placed at around 25 per cent. In other words, about that number of patients who are rendered asymptomatic by sulfathiazole are still gonococcus carriers and can transmit the disease to others. And, what with the thousands of patients who treat themselves with tablets obtained from druggists or physicians, and those who are dismissed as cured just because their symptoms are gone, one does not have to be a prophet to be able to predict the greatest epidemic of gonorrhea that our country has ever seen. We are in it now and there is far worse to come.

Without discussing pros and cons at length, some facts about this asymptomatic carrier state should be noted.

1 One of our large naval hospitals cultured gonococci from 23 per cent of their *males* who had been rendered symptom-free by one course of sulfathiazole tablets.

2 Mathis and Koch (Venereal Disease Information, Feb., 1944) obtained positive cultures in 32 per cent of a mixed group (male and female) rendered symptom-free by one course of sulfathiazole.

3 In this latter group 47 per cent had reached a persistently culture-negative state in one month after the positive culture, by the end of the second month 34 per cent more had become negative, by the end of the third month 14 per cent more had cleared culturally and 5 per cent were still positive after that.

Certainly, in these two experiences, and others that could be cited, one can find neither justification nor safety in the casual assumptions of "cure" based on disappearance of symptoms that so commonly return infected patients to their former pursuits to infect those who lend or sell their favors. He who weighs the matter in war and social values cannot escape a deep concern for the future.

#### WHAT CAN WE DO ABOUT IT?

There is some of our present grief, and just what can we do about it? We are in a wonder-age of medicine and we do not have to throw up our hands and answer, "Nothing." We can do a great deal about it if we will. We can make the best use of sulfathiazole possible and



where we have access to cultures we can use them—good cultures of properly secured materials will reveal by far the large majority of the asymptomatic gonococcus carriers. A few will escape detection by the usually advised three cultures. Where cultures are not available, one is thrown back on his clinical sense, and, by and large, whether he has cultures available or not, he might realize that neither he nor anyone else knows just when any patient is cured by these drugs. Therefore, he should be honest with his patients and himself and say so. Men do not want to transmit gonorrhea nor do many women above the prostitute or near-prostitute level. If told they may be running a grave risk of doing so if they have unprotected sexual intercourse during the first four months after the disappearance of symptoms, some will refrain and more of them will use condoms. In either

place in the scheme of things than just a means whereby the miracle-drugs could be obtained. And, believe it or not, patients actually went on to cure in that therapeutically dark age upon which the curtain was so summarily drawn about six short years ago. We even used local treatments during those days, as most of us seem to have forgotten. And some of us who used them gently and with good sense knew that they really promoted the patient's curative effort just as surely as we knew that those who used them roughly and unintelligently caused a great many needless complications and greatly prolonged the duration of infection. We didn't know the true mechanism of our stimulation of curative effort any more than did those who made applications to mucous membranes remote from the urogenital tract. We just knew it happened as did those who treated and still treat locally other mucous membranes.

Some of us were so stupid, or otherwise, that even when the rest of the world almost made them taboo we used them along with our miracle-drugs and some of us held off a little but resorted to them just as soon as there was the slightest evidence that the patient was not responding to these drugs. Not only this, but I have been told by many urologists that their disappointments had been so many that they are now using local treatment on all their males with gonorrhea and viewing sulfathiazole as a highly valuable adjunct thereto.

Evidently our urologists do not wholeheartedly agree with Berry (Urol and Cutan Review, Dec 1943, p 675) who summarily dismisses the matter with the statement, "Local treatment of the urethra is unsound in theory and unsafe in practice." After over thirty years of observation and gentle local treatment of gonorrheal urethras, I find myself more interested in results than in theory, and when I see such sweeping statements as the above I get the unkind feeling that things would be nearer truth if they read, "Any local treatments to the urethra are a nuisance for the physician and roughly carried out ones are a menace to the patient."

In other words, I strongly favor the gentle, sensible local treatment and abhor the others. I refuse to take the position that he who fails of response to sulfonamides and for whom neither pyrotherapy nor penicillin is available must sit around unaided by his physician until God in his mercy lets him get well by virtue of his own native curative responses, whether he be man or woman. It is too long a wait and too great a war and social menace.

Fortunately, for the present discussion, I am out of practice for the duration. This relieves me from all possible suspicion that the things I am about to advise are suggested because of their possible greater financial return. I have no financial interest in them. My sole interest is in the gonorrheic and his environment.

**Why Local Treatment Is Desirable.**—For the patients mentioned in

the immediately preceding paragraph, I am going to advise gentle local treatment whether they respond clinically to sulfonamides or not. Most of my reasons for so doing have been covered herein but, to avoid misunderstanding, I shall repeat them and add a few others.

1 There is a failure rate from the use of sulfathiazole that runs anywhere from 20 to over 50 per cent under varying conditions

2 There is an asymptomatic gonococcus carrier rate in those whose symptoms are banished by sulfathiazole that it seems reasonably safe to place somewhere around 25 per cent.

3 Gonorrhea has always been one of the greatest causes of lost-man-days among military personnel—and there is a war on

4 There are no universally available proofs of cure, and even with the best of them mistakes occur

5 Patients who become asymptomatic are often most casually dismissed, or dismiss themselves, as “cured” despite the above mentioned carrier rate

6 Even though the patient does not respond to sulfathiazole medication he seldom has the stormy disease course so common before its use in this disease. There is far less tendency for disease progression to other structures and of complications of gravity (In this statement I am considering the disease course in gently treated, co-operative patients and not disease course as influenced by rough treatment and poor patient conduct. Even in the presence of these latter factors he seldom reacts as he did in the old presulfonamide days.)

7 Treatment is sought earlier, more patients are seen in the anterior urethral stage, and most of them fail to have a posterior urethral extension if they immediately are placed upon sulfathiazole

8 Of all gonorrheal areas the anterior urethra is most easily and safely treated and if roughness of procedure and high fluid pressures are avoided no complications will be caused by it.

9 More care and judgment are required for the treatment of posterior urethral involvement with its concomitant prostatic infection, but even this is not beyond the intelligence and skill of the physician who knows that high fluid pressures spread disease and trauma to even the subacutely inflamed prostate gland does far more harm than good. There is a right and a wrong way and often a right and wrong time for most treatment procedures and it is here that the wrong way and time not only may produce irreparable harm to the patient but will and has discredited valuable procedures

10 And, perhaps most important for the day local treatment with the patient understanding how grossly the disappearance of symptoms may deceive makes the doctor king and not the tablet. Properly presented to the patients it often assures a reasonable period of post-sulfonamide observation. It will hasten the cure of the drug failure

as it unquestionably will shorten carrier states Above all things, it will protect society and it will add much to the credit of our profession

### A PRACTICAL PLAN OF MANAGEMENT

The decks being cleared, so far as my personal opinions are concerned, here is what I should do if I were to return to practice today I should give the admirable Army directive for the treatment of gonorrhea in males a decided twist or, perhaps more correctly speaking, I should use the two plans suggested for anterior urethritis together rather than wait until the patient devoted from five to fifteen days in proving that he had to be classed as a "drug-failure" I should take the time to make my patient understand just what the present situation is, in order to overcome the ideas the lay press or his friends have instilled into his mind, and I would show him how easily he might become a menace to womankind In other words, I should try to shift his mind from tablets to the value of local treatment, from symptoms to the nearest to safety now obtainable for this particular group of patients

And now, having perhaps overworked the "I should" idea, it might be well, for purposes of brevity, to resort to an outline of suggested measures, with parenthetical side remarks where they seem to be needed for clarity

**Anterior Urethritis**—1 Make a diagnosis by demonstrating the gonococcus by either the Gram stain or culture (Approximately 30 per cent of the patients presenting themselves for urethral discharge have a nonspecific urethritis and not gonorrhea If for any reason the laboratory findings have to be delayed, treat as though it were gonorrhea until proved otherwise)

2 Inject into the anterior urethra *not more than 6 cc* of either a 5 per cent mild protein silver or a 0.5 per cent strong protein silver solution and have it retained for five minutes If sulfathiazole does not check discharge give these treatments daily until the discharge stops, and every other day thereafter for two weeks longer If sulfathiazole does banish symptoms, give daily treatments for two weeks and on alternate days for at least two weeks thereafter (The capacity of the average urethra is 10 cc The injection of fluids through an infected anterior urethra into an uninfected posterior one will precipitate many unnecessary posterior extensions of infection The constant daily use of chemicals in the urethra often will cause a continuation of discharge after gonorrhea is cured If patients cannot be seen daily give them a 1/8-ounce syringe or mark another syringe at the 6-cc point and let them use preferably strong protein silver because of its lesser staining propensities If the quantity does not exceed 6 cc he can do himself no harm with it.)

3 Prescribe 40 tablets of sulfathiazole and have him take 2 of them by mouth four times a day

4 After the five days of this medication, stop it for from three to five days and then give him a second course of 4 gm a day for five days, no matter how he may or may not have responded symptomatically (The asymptomatic gonococcus carrier rates previously mentioned were in patients responding clinically to only one such course of sulfathiazole.)

5 If symptoms persist after the second course of medication, forget the sulfonamides and rely upon local treatment (Do not, however, forget that indulgence in alcohol, sex excitation or sexual intercourse can be a cause of sulfonamide failure just as it can prevent nonsulfonamide-treated patients from developing their native curative responses. For which reason, blame irregularity of disease course on patient's behavior and you will be correct almost every time)

6 After the above program has been followed for anterior urethritis start to search for gonococci in the urinary sediment either by "smear" or culture and no matter how often the answer is negative, advise against unprotected sexual intercourse for at least three months—four months would be safer (It is true that most patients will not follow the advice to the letter but, if accidents do occur, they are not the fault of the physician. Patients who are assured they are well do not take it kindly if they later infect their wives or sweethearts. At least one such patient murdered his doctor.)

**Posterior Urethritis.**—The treatment of gonorrhea that has extended into the posterior urethra is not such a simple matter as when the infection is confined to the anterior urethra alone. It is here that ill-advised local treatments do most harm and, unless the physician is familiar with or will take the trouble to familiarize himself with the anatomy, particularly the vagaries of the external sphincter, the general behavior of gonococcal infections in this region and the ease with which local treatment can produce pathology that the gonococcus could not cause alone he had far better leave the whole affair to the patient's own curative responses. Time is not gained by insulting gonorrhea in this area by a lot of traumatic treatment such as high pressure intravesical irrigations and too early and too vigorous prostatic massage.

On the other hand he who knows what can be done when it can be done safely, as well as how to do it, can promote Nature's efforts to such an extent that the duration of gonorrhea from this point on can be cut in half.

All experienced physicians agree that no local manipulative measures of any type should be employed during the acute stage of posterior urethritis. They advise hot sitz baths and perhaps mild seda-

tives for the partial control of vesical irritability. Most of them insist that no local treatments should be resorted to until at least a week after complete vesical comfort has been regained. (One should not let this matter hinge entirely upon the presence of bladder irritability. Some patients with new posterior infections, though both glasses of urine are cloudy, are perfectly comfortable. Most of these, however, soon will develop the most atrocious vesical symptoms if intravesical irrigations are resorted to.)

*Hydrostatic intravesical irrigations*, as commonly employed, have been subjected to much just criticism and many have insisted that they be not used. Yet, many who condemn their use by others use them in their own offices to great benefit. Which, of course, means that, properly used, they are of definite value and improperly used they are a menace to the patient. The dangers come from too great fluid pressure and completely filling the bladder even under otherwise safe pressures. He who employs more than  $3\frac{1}{2}$  feet of fluid pressure or completely fills the bladder at even that pressure can expect a high incidence of epididymitis. He who uses catheters or Keyes-Ultzman syringes for the introduction of fluids into the bladders of gonorrheal patients should expect this and other complications.

The safe introduction of 1 7000 potassium permanganate solution into the bladder every second or third day unquestionably will hasten the time when one safely may approach the digital promotion of drainage of the prostate gland. He may reduce Nature's time at this stage by half but he gains no time if he introduces other complications. And he who is unskilled or too impatient to wait for cut-off muscle relaxation but persists in forcing it, had far better leave the job to Nature's good offices.

Whether one resorts to irrigations or not, the steady trend of such infections, *in cooperative patients*, is toward disease quiescence with its gradual disappearance of objective and, generally, subjective symptoms. The second glass of voided urine becomes clear and the first glass more slowly follows suit.

**Residual Infection in the Prostate Gland**—Sooner or later there arises the question of what to do about the residual infection in the prostate gland, and when to do it. The aforementioned Army Directive states that, "The second glass of urine should be clear for three weeks and the first glass practically so before gentle prostatic massage is started." This is rather dogmatic for a disease that so often shows exceptions and, though I was a party to writing the directive, I feel one should be a little more specific regarding the matter. So much needless pathology has been produced by too early and, often, too vigorous prostatic manipulations that there are many who have become unalterably opposed to their employment. I, personally, have

encountered so much of it I most certainly agree that the physician who cannot keep his mind on the end of his finger when it is in the rectum had better not put it there. He who cannot respect diseased tissue and realize that trauma should play no part in the treatment of this disease had better spend his time inspecting latrines, if he happens to be in the Services.

What is the value of the digital promotion of drainage to the prostate gland when properly carried out? Left to herself, Nature will take from three to four months to eradicate the gonococcus and aided by proper drainage promotion she usually will get rid of gonococci (if the prostate is the sole residual focus) in six or seven weeks. There will still be pus in the secretion but the gonococcus will be gone and, if there was not a focal infective prostatitis present before the gonorrhea was contracted, the pus cells will promptly disappear on further treatment. In the Services interest in the case appropriately stops when the gonococcus is gone. If they treated prostates solely because they harbored pus, just about one third of their personnel would need treatment and the war would have to stop or materially slow down. In civilian practice interest goes beyond the disappearance of the gonococcus.

Probably the safest view to take about the starting of so-called *prostatic massage* is that no one knows just when it is safe in any patient. We do know, however, that if done too early or too vigorously there will be a recurrence of urethral discharge and more or less clouding of the urine the next day and that we can use this as an indicator. If we confine our first prostatic manipulation solely to gentle pressure on the lateral lobes of the gland and there is a recurrence of symptoms we do not touch the gland again for a week. Thus we will avoid harming the patient. If after the next similar procedure there is no recurrence of symptoms, we can repeat it in three or four days and if this produces no reaction we are in all probability safe thereafter to carry out *gentle* prostatic stroking twice a week, which in my observation at least is better than treatments otherwise spaced.

When it is possible safely to carry out "massage" so as to obtain prostatic secretion for microscopic study the number of pus cells in the fresh secretion under the high dry lens should be counted. If at the end of six weeks of treatment this count has not reduced by about two thirds it is safe to say that the patient had a focal infective prostatitis before he acquired his gonorrhea. If this is to be cleared up it only can be done after the causal infections, usually tooth root abscesses, infected gum pockets or less often, infected tonsils, have received attention. To go on massaging such glands without attention to these causal foci is a waste of time, effort and the patient's funds.

Patients who have been carried through this regimen seldom carry the gonococcus unless there has been an infection of Cowper's glands or the seminal vesicles. Both of these are decidedly rare in patients who have not been subjected to high fluid pressures. The former almost invariably develop a very scanty urethral discharge lasting about two days in which the gonococcus is easily revealed following indulgence in alcoholic beverages or prolonged sexual excitation, and the latter have a profuse discharge containing the gonococcus after each involuntary sexual orgasm. All the older tests of cure again assume a value not holding for some time after sulfathiazole administration.

Where cultures are available, they, of course, should be used. In their absence microscopic studies of the washed urinary sediment of the first half ounce of urine passed immediately after digital stripping of the prostate, Cowper's glands, the seminal vesicles and anterior urethra are almost of equal value. And, no matter if all findings are negative, the physician is safest if he advises against unprotected sexual intercourse for the next three months. He does best to realize that gonorrhea is a disease of exceptions and that no matter what rules are laid down regarding it exceptions seem to occur.



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## CONTRIBUTORS TO THIS NUMBER

George E. Baker, M.D., F.A.C.P., Chief of Staff and Chief of Medicine, Memorial Hospital of Natrona County, Casper, Wyoming

Alvan L. Barach, M.D., F.A.C.P., Associate Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University, Assistant Attending Physician, Presbyterian Hospital, New York City

George E. Daniels, M.D., Clinical Professor of Psychiatry, College of Physicians and Surgeons, Columbia University, New York City

J. Louise Despert, M.D., New York Hospital and the Department of Psychiatry, Cornell University Medical College, New York City

Flanders Dunbar, M.D., Ph.D., M.D., Departments of Medicine and Psychiatry, Columbia University Medical Center, New York City

George L. Engel, M.D., Instructor in Psychiatry and in Medicine, University of Cincinnati, Assistant Attending Psychiatrist, Cincinnati General Hospital, Cincinnati, Ohio

Milton H. Erickson, M.D., Director of Psychiatric Research and Training, Eloise Hospital, Eloise, Michigan

James S. Greeno, M.D., Medical Director, National Hospital for Speech Disorders, New York City

I. W. Held, M.D., F.A.C.P., Attending Physician, Beth Israel Hospital, Diplomate, American Board of Internal Medicine, Formerly Clinical Professor of Medicine, New York University College of Medicine, New York City

Leland E. Hinsie, M.D., Professor of Psychiatry, College of Physicians and Surgeons, Columbia University, Assistant Director, New York State Psychiatric Institute and Hospital, New York City

Ferdinand L. P. Koch, M.D., Assistant Clinical Professor of Ophthalmology, College of Medicine, New York University, Ophthalmologist, Department of Ophthalmology, Third Division, Bellevue Hospital, New York City

Nolan D. C. Lewis, M.D., Director, New York State Psychiatric Institute and Hospital, New York City

## CONTRIBUTORS TO THIS NUMBER

- A. M. Master, M D , F A C P ., Commander, Medical Corps, United States Naval Reserve, Consultant Cardiologist, National Naval Medical Center, Bethesda, Maryland, and Cardiologist, The Mount Sinai Hospital, New York City
- John J. Moorhead, M D , D Sc , F A C S , Formerly Professor of Clinical Surgery, New York Post-Graduate Medical School (Columbia University), and Director, Department of Traumatic Surgery, Post-Graduate Hospital and Reconstruction Unit, Attending Surgeon, Post-Graduate Hospital, Medical Director, New York City Transit System
- John Romano, M D , Professor of Psychiatry, University of Cincinnati, Director, Psychiatric Service, Cincinnati General Hospital, Cincinnati, Ohio
- S. Mouchly Small, M D , Psychiatrist, National Hospital for Speech Disorders, New York City
- René A. Spitz, M D , Instructor and Lecturer, New York Psychoanalytic Institute, New York City
- Asher Winkelstein, M D , Associate in Medicine and Chief, Gastro-intestinal Clinic, Mount Sinai Hospital, Associate in Medicine, Post-Graduate Medical School, Columbia University, New York City

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### SYMPOSIUM ON PSYCHOSOMATIC MEDICINE

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#### A CLINICAL DESCRIPTION OF PSYCHOSOMATIC MEDICINE

LELAND E. HINSIE, M.D.\*

##### I THE PROBLEM

LIVING as a human being often takes more energy than the daily tasks that gain us a livelihood. It is easier to get settled in an occupation than it is to adjust ourselves to the personal side of people. It is one of the peculiarities of man that when his energies cannot be essentially externalized, they dam up within him, within his mind or body or both. The persistent damming up leads to tension and symptoms. When the symptoms are in the mental sphere, they give rise to special names, such as psychosis and psychoneurosis. When the tensions of living localize themselves in different parts of the body, it appears that the organic part involved is the seat of the trouble—that is, the organ appears "diseased." In a broad sense of the word it is diseased—it is deprived of ease—it is disordered functionally, but the trouble stems from unhappy adjustment to life and not from such organic sources as bacteria, injury, etc.

From time to time the physician is baffled by the failure of a patient to respond favorably to a course of therapy that ordinarily brings about recovery. The patient, for instance, when first seen gave a clear-cut history of a peptic ulcer, the physical findings supported the history. The course of therapy was clear and the patient sincerely followed all instructions. Yet, after a few months of careful cooperation the symptoms are essentially unchanged. The doctor is genuinely puzzled; he surveys the entire situation again, everything is correct—diet, rest, medication; the patient has meticulously followed all. Maybe consultation with a surgeon is in order. It is held. Nothing new develops.

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\* Professor of Psychiatry, College of Physicians and Surgeons, Columbia University. Assistant Director, New York State Psychiatric Institute and Hospital.

The patient's general condition grows worse. The symptoms are now such that she spends a long time in bed, lately her husband has had to prepare his own breakfast, for his wife is too weak to get up. More recently he has had to prepare lunch and dinner, he has had to do the marketing. He has also had to do the housecleaning. She cannot eat at the table with him because the sight of food is nauseating.

The couple do not invite company any longer because of the wife's condition. And, besides, the wife is getting irritable. The children are neglected, they too are changing for the worse because now neither parent can give them attention.

Surprising, says the doctor. Something is wrong. A peptic ulcer should not disrupt everything in the household, should not fray the dispositions of all members to the point at which the household should be dissolved.

Somatic medicine, so to speak, has fallen far short of a cure. All the doctor's skillful prescriptions, the ones that have helped so many other patients with a similar condition, have been without avail. The ulcer does not heal.

On his next visit the doctor, knowing that a repetition of the hackneyed examination that he has so often performed would be without results, begins to ask the patient how she feels as a person, as a human being who is trying to get something out of life. The patient is surprised at such a topic of inquiry. What have her life efforts got to do with a peptic ulcer? Still, she senses that, even if the subject is irrelevant, here is the first person in her life to ask her how "she" feels. Up until this time she has been a peptic ulcer. The strangeness of her situation in life begins to dawn upon her. That's right, she thinks, I've become a peptic ulcer.

"Doctor, maybe that isn't so surprising. I'm suddenly overwhelmed with a composite picture of my past. I never was what I wanted to be. If I'm a peptic ulcer now, I was something else then, yet, it all adds up to the same thing, a disappointed and frustrated life, one always devoted to the needs and demands of others. Maybe it sounds odd, but I was not I. From my earliest years I was known as the 'little mother' around our house. I was pleased with my role as a housewife, for it occasioned considerable approbation, still, I yearned for the fun and freedom of a child.

"Mother was kind in her strictness. I didn't know it then, though later I realized what a sacrifice she was to life and living. She lived only for father and me and the house. What am I talking about, doctor? That's been my life, too.

"When I came into adolescence, I often thought overtly of breaking away. I knew I wasn't living. I was an automaton. Capable in school. I solved scholarship without trouble. But, I couldn't solve human relationships. The girls in my classes seemed to admire me, I

helped them with their school work. Outside of classes, though, I was alone. Girls of my age seemed to pity me in a way, pity from a distance, no closeness, no nearness. It's what I said a little while ago—nobody ever asked about me, about how I felt. They asked about my mathematics or languages or geography. The only difference today is that they ask about my peptic ulcer.

"While in high school I decided to become a career woman. I remember feeling heroic about the choice, a sort of heroism stemming from resignation. If I couldn't be a human being, I could be some kind of an efficiency expert, detached, cold but capable. I grew into so-called maturity with scholastic ability but beneath it all I didn't like it. It was a screen against the expression of human qualities and an effective, though a harmful screen. Over the years I grew tense, critical, misanthropic. With grim humor I labeled myself a success.

"Then a man came along. He was kind. He said he liked my type because he too placed his profession above all. We talked of love. We never quoted ourselves, our feelings about love. We quoted the literature, letting it be half-known that it was from the literature, hoping that it would appear to come from our own hearts. It was beautiful, even though it was impersonal. Love doesn't thrive with a mouth-piece. We knew that, for we talked about it at length.

"Tension, more tension. The nature in me yearned for expression. I fed it on scholarship. I was tense inside, in fact, I felt the discomfort mainly in the stomach—it felt as if it were knotted up. I lost the zest for eating, lost weight, felt weak. It was just as if my feelings went to my stomach and couldn't get any further.

"But, this is all so foreign to the cause for your calling on me. Yet is it? I seem to have gotten back to my stomach, but this time by a different route."

For the first time since he had been called in to treat her, the doctor noticed how animated she was and how relaxed as if a great burden had been lifted from her. After a pause, he gave a sort of a simple lecture. Parts of the body—the stomach, for instance, can be upset from one or more of several causes: he mentioned dietary indiscretions, bacterial troubles, chemical changes, anatomical anomalies, deficient blood supply, altered nerve activity and disordered emotions. He said that careful examinations in her case had ruled out all save the last and she had made out a clear case for the last.

The doctor cited from his clinical experiences to show how emotions can be bound to any organ of the body, whether that organ is organically sound or disordered. He showed how sick organs, particularly those belonging to the vegetative system, can be prevented from healing when the patient's emotions flood the organs. Today the term *hypochondriasis* is a household phrase meaning an "imaginary" physical ailment. It is 'imaginary,' however, only in the sense that the or-

gans are not disordered in the way that the patient believes them to be. The term pathology is enlarged to include abnormal emotions. Hence, it is said that the organ shows psychopathology. Within recent years this point of view has been subsumed under the general heading Psychosomatic Medicine.

Every disorder of the physique is represented to a greater or lesser extent in the mind of the patient. In many instances the mind plays an excessive role, so to speak. In other instances the mind plays the exclusive role, as it does, for example, in conversion hysteria. In the latter case there is usually a well-recognized "gain through illness." The youngster develops a headache just before leaving for school, the connection may not be seen, but there is a test in mathematics that morning. Or, the young lady, who does not like the pressure brought upon her by a suitor, wards him off with alleged physical complaints. Or, the wife, finding married life incompatible, becomes "a chronic invalid." Or, the laborer, unwilling to work steadily, seizes upon the gain through illness and becomes a prolonged compensation case. Or, the soldier, fearful of death, develops paralysis so that he cannot participate in battle.

Over several therapeutic sessions the doctor put the foregoing thoughts in the mind of his peptic ulcer patient. She talked at length to him.

"I became his fiancée. I wasn't at all prepared to share feelings with another, because I had trained myself almost entirely along intellectual lines. The courtship was beautiful, founded as it was on amorous quotations from several sources, but not from us. Still, I was happy in an illusory way. Not altogether so, however, because I had found myself in the business world. I was doing a better job than the man I replaced. Often I shuddered, though, when I realized I was a better man than a woman. My fine clothes were a pretense. But, the woman in me never gave me rest. It beset me from many sides. I grew tense. My appetite was poor, my stomach was usually upset. I even guessed that the woman in me was being dammed up in the stomach. My friends knew it, without realizing that they knew it, for they often told me that I was all work and no play, that I should affiliate my interests with men, in short, that I be a human being as well as an efficiency expert.

"We married. I only knew intellectually how to be a wife. My husband was little better. He was a scholar above all. Our social contacts were based on intellectuality. When we had a couple at the house for an evening of bridge, that's all we got out of the evening, bridge. Our vacations were itineraries, devoid of human interest, full of intelligence. Quiet evenings at home were supported by heavy literature.

"How I hid myself from myself! Whatever feelings I let loose came out vicariously in words. It was a terrific conflict that griped me, griped my stomach. That's just where I felt it, in my stomach. My

stomach was the stopping place for my emotions I'm sure I made my stomach sick, so that it couldn't work properly. If I clenched my fist violently for a long time I'm certain it would alter the blood supply to the hand, it would lead to skin changes, like little ulcers. Feelings can lead to ulcers, for do they not cause tensions, constrictions? All the x-rays showed spasticity.

"As the months of married life went by, I secretly wished to get away from it all. I saw my husband less and less of the time, because, as we incorrectly assumed, he was building up a professional career and was busy day and night. In one respect I was like a single woman again. But I didn't want that either. Conflict! Stomach! Ulcer!"

The patient steadily improved. After each psychotherapeutic session she could feel the release of tension in the stomach area. Now the routine physical treatments could act favorably. Gradually the peptic ulcer disappeared. Psychotherapy continued, however, for a longer period, until such time as their lives could be rearranged to the point where both husband and wife were human beings as well as machines.

The treatment was psychosomatic. We may not know how emotions get crowded into an organ or an organic system, but we know they do, and we know how destructive the results can be. The proof to date is established pragmatically: for, with the release of tensions associated with habits of living, symptoms disappear. How often have we seen the symptoms of appendicitis continue long after the appendix has been removed years longer! We've seen those same symptoms removed by psychotherapy.

It seems odd in a way that one's position in life can change one's physiology and lead to organic pathology. Yet, we know that deep grief, for example, may lead to anorexia, insomnia, inertia—all of which if of sufficient duration can produce marked physical changes.

This is the type of psychosomatic medicine that any physician can and should practice. It is simple and usually effective. Be a good listener, not alone to the body, but to the human being who has the body.

In the majority of instances, you do not have to be a psychiatric specialist though a little more formal knowledge of the whims of emotions would add considerably to the comfort of your patients.

To what sources should the physician go to get enough psychiatric background to grasp the practical application of concepts in psychosomatic medicine? The literature is beginning to be extensive yet the principles as they are known today are presented in a simple and clear manner by Wers and English in "Psychosomatic Medicine" (W. B. Saunders Company, Philadelphia and London 1943) the subtitle of which is "The Clinical Application of Psychopathology to General Medical Problems." The title may sound a little formidable. It should not for it is only an abbreviation for what has been known in clinical

practice for centuries Psychosomatic means "relating to the mind and body" It incorporates the age-old concept that sickness affects the person and the person affects the sickness Physicians should not shy from the subject with the unwarranted belief that psychosomatic medicine is something new and untried and that, therefore, they will wait until its real, practical application to the patient is established It is an established practice All the great clinicians of the past stressed it

The scientific approach to psychosomatic medicine has been greatly facilitated by advances in organic and mental medicine The epochal researches of Freud give the physician of today a workable, scientific form of psychotherapy, one that can be used by any physician To be sure, the technic of psychoanalysis can be applied in its highest form only by those who are highly trained, yet its principles can be adequately used by any physician, particularly in that large group of patients to whom the term *psychosomatic* is directed

Weiss and English repeat the opinion of many when they say that "between the small number of obviously psychotic persons whom a physician sees and the larger number of patients who are sick solely because of physical disease, are a vast number of patients who are not 'out of their minds' and yet who *do not have any definite bodily disease to account for their illness* Psychosomatic medicine is chiefly concerned with them (Group I) It is reliably estimated that about a *third* of the patients who consult a physician fall into this group These are the so-called purely 'functional' problems of medical practice

"Approximately *another third* of the patients who consult a physician have symptoms that are *in part dependent upon emotional factors*, even though organic findings are present (Group II) This second group is even more important than the first from the standpoint of diagnosis and treatment "

The third group "comprises a group of disorders generally considered wholly within the realm of 'physical disease,' which have to do with the vegetative nervous system, such as *migraine, asthma, and essential hypertension* Psychosomatic medicine is much interested in these disorders because it believes that the psychic factor may be of great importance in their etiology, and, even more importantly, in their management "

## II LEVELS OF GROWTH OF THE HUMAN MIND

Every organ and organic system has function The gastro-intestinal tract serves alimentation, heart and blood vessels circulate substances to various parts of the body, kidneys serve elimination, bones form the framework, muscles serve motility, the nervous system coordinates, the totality of these systems, and others, constitute the organism as a whole, so to speak The organism is destined to move about a very complicated environment, to become an integral part of it It starts off

essentially as an organic being and for the first few years its parents act in its behalf in almost all matters, save the purely vegetative. In these early years the mind is budding and it is significant that the mind is made up of components from two general sources, the instincts and the parents. The wholesome child is the one whose training by the parents is in harmony with the environment, on the one hand, and with the instinctual urges, on the other.

Soon the *personality* begins to develop. Presumably the personality (or the psyche, or the mind) is an outgrowth of cerebral activity, it is a function of the brain. In the early months of living the two cannot be differentiated, but, as experiences accrue, the personality grows and grows until it has its own form and functions, which are quite different from those of the brain itself though it never loses its original embedment. The mind (or psyche or personality) may be likened to a tree rooted securely in the earth, yet having its own distinctive qualities fed by the earth, but also by the atmosphere or environment. The tree has its own form and functions, which can be understood not in terms of the soil (brain) alone but particularly in terms of its own qualities and its environment (sunshine, rain, winds, lightning, etc.).

#### 1. THE SOMATIC PHASE

The human mind passes through levels of growth, so to speak. In the beginning the acorn and the soil are as one piece. In the early years of growth the child's mind is made up largely of a knowledge of its physical self and its physical surroundings, reinforced by the instincts which too are largely physical or physically expressed. To designate this level of growth it is said that the mind is essentially *somatic* in its composition. Some people never get well away from this level of adaptation. They meet the environment chiefly in terms of their own organs and organic functions. They become the hypochondriacs, whose socialization is heavily burdened with their organs, their organic functions. When you ask them how they 'are', they take 'they' to mean their heart or lungs or stomach or whatever organ or organic system may be involved. These people do not speak for themselves, they speak for their physiology.

Human beings get extensive training in converging their interests, their emotions upon their organs. It's their first training period, normally it lasts a few years, though in certain families it may be a habit pattern of a decade or more. This is particularly true when the teacher, that is, the mother or father, is preeminently hypochondriacal. A *self on triax* may and often is fostered by an originally weak and by sustained illnesses. The human being gets extensive a knowledge (good or bad) of his body. Emotions, substantial pathway to and through the organs of the body and abdominal viscera are predominantly involved.

It is in this early period of growth that the habits, called psychosomatic, gain their best training. It is in this phase of growth, too, when the child is most closely taken care of by its parents. It's a stage of relative ease and contentment, without pressure from the extraparental environment and milieu. Some individuals (hypochondriacs) never essentially abandon the habits of this period. They go through life as children, always looking for the kind parent. They are as parasitic to the physician, for example, as they were to their own parents.

Hypochondriasis that perpetuates itself with perhaps only slight modification into and through adulthood does not respond favorably to therapy. It is an habitual pattern. Another reason why therapy is usually ineffectual lies in the consideration that other, later, more mature patterns are poorly developed. If you take away the hypochondriasis, there isn't anything else strong enough to support the person. The patient knows that and defends himself, perhaps rightfully, against any effort to remove his essential prop.

When, however, hypochondriasis is a phase to which an individual reverts in order to escape from some later type of growth, to which he had more or less successfully adapted himself for an essential period of time, it is often possible to assist him back to the higher level. In these instances the psychosomatic approach will likely produce favorable results, because the patient is not habituated to the somatic type of emotional expression, but has simply fallen back upon it in order to escape a difficult situation, at some other, higher level of growth. Moreover, in these cases as a rule, the diversion of emotions into somatic channels is not diffuse, but is restricted to a single organ. One then speaks of an *organ neurosis*.

Organ neuroses are common in general medical practice. The psychotherapeutic approach to such states has already been described in a case with peptic ulcer as the presenting symptom.

The neurotic component, that is, the emotional conflict, may attach itself to an organically sound or to a pathological organ. Quite apart from the state of health of the organ, the psychotherapy is the same for both. The type of organic therapy to be administered will, of course, depend upon the nature of the organic involvement.

There is a special type of hypochondriasis engrafted upon the hysteroid personality. It is commonly known as *conversion hysteria* and includes one or more of a welter of symptoms—such as anesthesia, paresthesia, paralysis, paresis, loss of function of one of the sense organs (blindness, deafness, etc.), nausea, vomiting, aches in various parts of the body. These, too, may be called organ neuroses. They occupy an unusually favorable position from the point of view of therapy, probably because they occur in individuals who in many respects have often achieved at least fair to middling adaptation to adult levels of behavior. Furthermore, hysterical symptoms are ordinarily episodic.



in appearance and are "used," so to say, only when the adjustment to the higher levels fails

Another form of hypochondriacal expression, one that seems to be losing vogue diagnostically, is *neurasthenia*. It is characterized by easy fatigability, both mental and physical and by a variety of symptoms secondary to fatigue. Patients in this group usually fail to respond favorably to psychotherapy. There is a growing conviction that further research may place the etiology of this disorder in the organic sphere, perhaps under the heading of anomaly of the vegetative nervous system and its adnexae.

The diversion of emotions to organic channels of expression is almost a universal phenomenon among the group of patients with *schizophrenia* or *dementia praecox*. While a great deal is known about the psychopathology of these patients, little can be done therapeutically when the emotions are thoroughly fixed to the organs. Schizophrenia is said to be a regressive mental syndrome, but in many instances it is not regressive for the reason that the individual never did adjust himself well to higher levels. He has little to regress from so to speak. Others who have attained some measure of success may benefit through psychotherapy, especially if they are not too frightened by the ordinary demands of reality.

Since we are presenting here a point of view rather than an organized classificatory scheme it seems unwise to mention other clinical states in which hypochondriasis may appear. We should like to close this section by repeating what was earlier said, namely, that it is natural to the growth of all human beings to pass through a relatively prolonged phase of growth during which the infant's attention is appreciably converged upon the structure and functions of his bodily organs. As we put it earlier, every human being experiences much training in matters psychosomatic. Often the training determines later adaptation to life, often it is the phase of growth to which maladjusted individuals revert. Psychosomatic therapy must include a survey of the early years of growth within the family circle.

## 2. THE NARCISSISTIC PHASE

The second phase of growth consists largely in the expansion of the child's ego. This process usually starts in the neighborhood of the third year when the child begins to get a large quantity of praise and commendation for good behavior. Verbal and material awards are given for cleanliness, good table manners, politeness, obedience, intellectual display, and so on. Indeed, at no other time in life will this individual get such pure acclaim. He is often made to feel that he is omnipotent and omniscient. The parents, perhaps also grandmothers and aunts, gather in formal silence to hear the new words of wisdom or to witness some remarkable act. Laureates are earnestly requested

Much of the child's energy, formerly devoted to his physique, now moves on easily to the realm of the ego. It is more profitably used there. This is the phase of narcissism or self-love in the ego sense. It is nurtured by the parents for years to come and is one of the strongest ties between parents and child. It is one of the bonds, indeed, the strongest, from which to extricate oneself. It is difficult for normal children to reduce its intensity and it is usually impossible, except through psychotherapy, to do so with those who are anomalous or abnormal in personality development.

We can only mention in passing the many pitfalls that the child may meet. He may be an unwanted child by one or both parents, or they may bring him up as a girl, or he may be early orphaned and brought up by a maiden aunt, or one of the parents may die or leave the family, while the child is young, or one or both parents may be overdevoted to him and cling to him for years. The possibilities are many. We should not forget that the child himself may be unable or unwilling to go on to the next stage of development.

Narcissism, however, in and of itself, is not a psychosomatic problem, but because it is such a close outgrowth of the stage of somatism or body interest, whenever the subject's narcissism is injured (and narcissism is often fragile in the hands of others), the pathway to somatic complaints is short and easy to traverse.

Usually psychosomatic complaints, or should we say physical complaints of mental origin, when seen in the narcissism of hysteria are amenable to psychotherapy. When they are implanted in the schizoid personality, they are more difficult, if not impossible, to remove.

Merely to complete this little survey on narcissism, though basically it is not connected with psychosomatic medicine, it might be mentioned that the compulsive-obsessive form of psychoneurosis is believed to derive most of its unconscious components from the stage of narcissism, although not a few such patients also show some conversion symptoms. Psychotherapy in these cases is, however, largely concerned with the mind and not the body.

### 3 THE SUIGENDERISTIC PHASE

The third stage of personality development, beginning at the end of infancy (fifth year) and terminating at or around puberty, contains elements of the past (somatism and narcissism), to which are now added more or less extensive experiences with members of the same gender. This is the stage of initial socialization and the child spends the years from infancy to puberty, affiliating his interests principally with members of his own gender. That is why the term "sui (one's own) genderism" is used to designate this phase of growth. In the human being the preparation for maturity extends over years. About the first five years are spent in getting used to oneself, physically and

mentally. Of course, this process never ceases. The next six or seven years are spent in getting used to others. To make the latter step as easy as possible the child adapts himself for a long time mainly to members of his own gender. In the meantime he acquires parental substitutes in the form of teachers (scholastic, religious, recreational, etc.).

Usually the associations with one's own gender in this period are nonsexual, but among those who are later to show difficulties in adjustment, the background for homosexuality is laid. Sex first appears during the period of infancy and is directed to the parents, to whom the infant takes all his problems. In the late infancy period he converges his sexual interest upon himself. During the latency period (from infancy to puberty), the child's sexual interests undergo partial sublimation but a large share of it is externalized upon members of the same sex. When the sexual interests are well sublimated, the term *sui-genderism* is used, when they are expressed in nonsexual, but amorous ways, the term *homocrotism* is employed, when the interests are overtly sexual, one speaks of *homogenitalism* or *homosexuality*. Ordinarily the three types of activity appear in the latency period. Subsequent personality growth depends in large part upon the degree of fixation of interests obtaining in this period.

While the majority of individuals relinquish *sui-genderism* in favor of *altrigenderism* (the state of being interested in the other, opposite gender) a certain proportion do not make the change. Some remain overtly homosexual. These people usually have no conflicts about this way of adjustment. Others with overt homosexual experiences try to get away from homosexuality through marriage. These people commonly run into trouble, a fair share of marital incompatibility is based upon this difficulty. Still others can give vent to their homosexuality only under special conditions such as alcoholism and drug addiction. A final group remains the members of which try to keep their homosexuality in deep repression. The repressed homosexuality is so strong, however, that it cannot be kept repressed; it comes out of the unconscious in the guise of symptoms. An outstanding example of the latter is seen in the paranoid form of schizophrenia, the core of which is founded upon delusions and hallucinations of persecution by members of the same gender; often the persecution appears overtly sexual.

The general medical man does not have much to do with those homosexual individuals who express their troubles through psychotic manifestations. He soon turns those problems over to a psychiatrist. But he often sees those whose troubles are fundamentally homocrotic. However, the patient does not go to the physician for correction of his homocrotism. Too frequently the patient does not see his own problem clearly or if he does he makes an effort to conceal it. He usually presents a physical complaint to the physician. The physical complaint is usually a disease though neither the patient nor the

doctor may recognize it as such. Ordinary medical means fail to effect a cure, the symptoms persist in spite of good medicine or surgery. An investigation into the living habits of the patient soon reveals psychopathology, namely, that there is considerable incompatibility with the wife, she berating him for his ever-growing passivity to her, he spends most of his time with male companions, he is increasingly irritable to her. He claims that he is very fond of his wife and that it would be pathetic if they had to separate. During further interviews it is established that he married more or less precipitously in order to escape from too close affiliation with men.

Treatment now progresses along both psychical and somatic channels. As the patient gains understanding of his original difficulties, the somatic problem that failed to improve under medicinal or surgical therapy gradually clears up.

#### 4 THE ALTRIGENDERISTIC PHASE

The fourth phase of personality growth, starting in early adolescence, is called the altrigenderistic, it refers to adaptation to the opposite gender. This phase, too, takes years for adequate development. There is little wonder that so many marriages are discordant. Nature must have realized the difficulties attendant upon harmonious marriages, for she extended the period of preparation physiologically up to twelve or thirteen years, to which our legislators add another half dozen years. Yet, overt incompatibility leading to a separation of the parties is relatively uncommon, due in part at least to the generosity of the partners, who usually let the other one fall back upon his or her daily activities. Which is but another way of saying that the partners fall back upon their own narcissism. Usually, however, there is enough altruism to keep the marriage harmonious.

There are very few psychosomatic problems in husbands and wives who get along well together. Those that do appear are mild in character and of short duration.

#### 5 THE PHASE OF ADJUSTMENT—THE IMPERSONAL SIDE OF LIVING

The fifth phase of growth, not comparable chronologically with the other four, starts early in life and is continuous throughout life. It constitutes adjustment to the essentially impersonal side of living, including scholarship, career, recreations, hobbies, and so on. Some individuals, who cannot get along in intimate relationship with people, can meet people very happily by way of their job or career. They personalize their work, so to speak, and they get along well on the basis of personal contacts professionally guided. Others break under the all-work-and-no-play regimen. The latter may ascribe their difficulties to overwork. Overwork, however, is too frequently an effect and not a cause. Psychosomatic problems among the overworked are not un-

common Reduction of hours of toil cannot in itself effect a cure, unless the individual can learn to be a human being among human beings when he is not at work.

### III THE PERSON IN THE BODY

**Personality Defined**—When we speak of the character or disposition of a person, we have in mind the organization of his ideas and feelings. The latter are systematized, so to say, they are arranged into a more or less habitual pattern for the given individual, for brevity's sake we call the totality of his ideas and feelings his personality. His personality is the medium through which he establishes relationships between himself and the environment about him, it is the agency through which he expresses his inner wants to the world about him and through which he receives impulses from without. Perhaps this can best be illustrated by reference to the original meaning of the word "personality." It stems from the Latin *persona*, which was "a mask anciently worn by actors, covering the whole head and varying according to the character to be represented." It is broken down still further into *per* (through) and *sonare* (to sound). The personality is the medium through which pass impulses from within and without.

It is not strictly true, however, to conceive the personality as a bridge between the person and his environment, because the only way that the personality can let itself be known is through the organs of the body. Emotions and ideas cannot reach externality save through tissue. Since body tissue is the great conveyor of the impulses of the *persona*, it is understandable that, when we consciously refrain from acting out an urge, the energy of the urge gets held up in the given tissue. The greater the urge that is repressed the more keenly is the body sensation felt, until the subject comes to regard the body sensation as a physical illness. He usually fails to recognize that the body is ill because he unwittingly flooded it with an inordinate quantity of emotional energy.

A young man unduly shy and reserved fell in love with a girl but he was too repressed to let her know it in any way. As his love grew it steadily dammed up within him. He tried to deny to himself that he loved. He began to lose appetite, then to feel sick to the stomach. His feelings were transferred in increasing quantity to the stomach. His feelings gradually left the girl as they were added to the stomach. Examinations by the doctor failed to elicit any organic etiology. A review of the emotional life of the patient soon uncovered the nature of the stomach disorder and psychotherapy released the emotions from their unwholesome attachment. The stomach trouble was cured though it took a much longer time for the young man to follow the doctor's instructions regarding healthy contacts with the environment.

There are several types of personality. The type itself does not

necessarily indicate abnormality. One person may be quiet, reserved, taciturn, yet he may not be at all troubled by his personality. Another one may be lively, talkative, frank and open, but he is well adjusted to himself and to others. A third person may be self-contained, conceited and highly interested in himself, yet he is at ease with himself and does not cause discomfort in others. A fourth is a faddist on health, yet he is not disturbed by his enthusiasms, nor does he try to impose his interests upon others.

**Distorted Growths of Personality**—As a rule, it is desirable to treat the personality when it becomes extreme in its manifestations, for it is then that the personality is not helping, but is hindering, the individual. It is a valuable working hypothesis to look upon the personality as a distinct part of the human being, as an organ of the body, if you wish, an organ that has heritage, embryology, anatomy (gross and microscopic), physiology and pathology. The personality can have poor hereditary potentialities that may cause it to wear out in the early years of life, in somewhat the same manner that a constitutionally weak kidney, for example, undergoes involution early in life. A weak personality can handicap a career every bit as much as a weak body can.

Or, a constitutionally strong personality may be famished by poor nourishment. It is not a figure of speech to speak of emotional anemia, there is little that is more destructive to the full life of a child than an unloving parent. A child needs affection just as much as it needs nutriment. This was recognized centuries ago by the lexicographers who formed the words *nurture* and *nourish* from the same root word. To nurse, to nourish, to nurture—all have the same origin. Nurture expresses "thoughtful care and moral discipline." It may not be amiss to see in these words the close bond between the mind and the body, to see, in other words, a cogent psychosomatic parallelism.

It is equally injurious to the growing personality to have a plethora of emotions imposed upon it. In *School for Scandal* Sheridan wrote that "your character at present is like a person in a *plethora*, absolutely dying from too much health." Jeremiah Taylor expressed the same idea in these words: "At the same time he is full and empty, bursting with a *plethora*, and consumed with hunger." The overindulgent parent compels the child to gormandize, to take in excess that which is forced upon it. In so doing, the parents distort the natural flow of secretions, which is but another way of saying that when parents do everything for a child they fail to give the child the opportunity to express his own natural self. The child's own inner needs are sacrificed upon the altar of greedy parents.

These are not new ideas by any means. Every doctor, every person knows that these things can and do happen. What we need to know, however, is that these distorted growths of personality are very frequently reflected in the organs of the body in the form of organic

symptoms for which there is no recognizable organic cause. The sufferers go to a doctor with physical complaints. Some of them do not know that the physical complaints are but mere disguises for mental complaints. Others have a vague opinion that there may be a connection. It is traditional, though, to conceal unhappiness and unfortunately many physicians conspire with the concealment. It is as though the physician thinks that unhappiness can be lived out only through the mind, when at a moment's reflection he can recall several of his patients whose physical symptoms disappeared after a good heart-to-heart talk.

Psychotherapy is not, of course, as simple as that, save in a few instances. Psychotherapy has to be better organized, has to be more comprehensive, in the vast majority of patients.

**Types of Distorted Personality and Their Treatment**—There is a large group of patients for whom the doctor, not a specialist in psychiatry, can do much good. In what is to follow there is a thumb-nail sketch of types of personalities that can be easily identified by the physician, personalities in whom there is very often a shifting of emotional troubles to physical areas (heart, lungs, stomach and so forth). Treatment of the personality, when undertaken early in the illness, often leads to good mental and physical health.

### I SCHIZOID PERSONALITY

Some children are born quiet and reserved; others acquire those traits, while still others have them thrust upon them. In each instance, however, the traits are modifiable to a greater or lesser extent. The schizoid individual is an *introvert*, a quiet, seclusive, taciturn person who is ill at ease with people. He gets along far better with the inanimate world, though he is able to meet others by way of intellectual rapport. He finds it very difficult to emotionalize his interests, unless he emotes upon the impersonal. He may be communicative as regards his intellectual pursuits, but he seldom reveals anything about himself as a human being with deeply living feelings. Usually he leads a rich phantasy life, which, however, he keeps to himself and it is into his phantasies that he pours his feelings. His feelings remain within him; he is introverted. The schizoid individual is prone to divert his emotions from his phantasies into one or more organs or organic systems; that is, he is inclined to be also hypochondriacal. His hypochondriasis is often regarded by him as the real reason why he does not spread his interests among people, why he does not participate in recreations. If he has a hobby, it is of the lonely type, or, at least, he makes it so.

The schizoid person seldom goes to a doctor for his schizoidism. Rather, he presents the organic aspect of his trouble, for which, of course, no organic cause is detectable. Medicines may be taken for months or years, yet the symptomatology remains unchanged. After

surgical operations—let us say, after an appendectomy—the course of the complaints is the same as it was before the operation. While the stomach is a favorite organ in which to lodge the emotions, the eyes and nose run a close second. The best talents of the ophthalmologist and rhinologist fail to remove symptoms for the simple reason that neither lens nor resection of a septum touch the emotions. It is only too well known that “sinus” (of hypochondriacal origin) survives all medical and surgical skills, indeed, the latter lend plausibility to and perpetuation of the symptoms.

When shut-inness (schizoidism) grows progressively more intense, it is not unlikely that it may lead to schizophrenia (dementia praecox). The need for psychotherapy during the stage of schizoidism is obvious.

**Treatment of the Schizoid Personality**—*A slow and steady habituation of the emotions to natural environmental interests* is the core of treatment. The subject should align his interests with a group or two, perhaps, it might be well to have him join some informal educational group, the kind that serve collations with their scholarship, so that he might be gently introduced to the human side of life. It must be remembered that the schizoid person is afraid of human relationships, often as afraid as the normal person is of some real impending catastrophe. He really is. He should not be hurried. If you hurry him you may have to treat his “sinus” for a much longer period than you would treat his personality.

He should affiliate his recreations with others. If stamp collecting is his hobby he should be encouraged to socialize the hobby, to make it a means of meeting people for more than philatelic reasons. It is not unlikely that he may come to feel at ease with some eligible young lady via stamps. And the interest in her may bear that imprint for a long time. Don't hurry him. Falling in love (without stamps) is one of his most difficult tasks. If it is forced he may recoil and fall back upon his “sinus.”

It is a grave mistake, one that is repeated daily, to advise a schizoid individual to “go with a girl.” The advice is not only gratuitous, it is injurious, for the result is usually a shocking failure. This person, perhaps more than others, needs months of training and experience in ordinary social amenities before he is ready for intimacies.

*He must be gradually weaned from home and parents*, particularly from mother. Don't be discouraged if progress is slow. Remember that nature allows about twenty years to cover the transition from mother to another girl and another home. You ought to allow at least a year. If you don't, you'll be treating the “sinus,” if not something more disabling, for years to come. Patience is the keynote. The instincts will protest against delay, they don't know the pitfalls of premature hurry. Instincts destroy what they would best preserve.



*Direct psychotherapy* must be carried out at the same time. Encourage the patient to tell you about himself, about everything that has gone into his life. It is notorious how poorly learned these people are in matters of ordinary life. They have shut their eyes to human nature and have constructed their own meaning of what they observe about them. Usually they grow up in a detached sort of way. The "knowledge" they have of human relations is a product of their imagination. The physician can do much to clarify the physiology of the mind, of the body, of the herd, of the society in which he lives.

This all-too-brief delineation of the schizoid personality is intended to show the relationship between the person and his organic symptoms, and to show the way to a psychotherapeutic approach. It indicates a psychotherapeutic approach that can be used by any physician in the treatment of early psychosomatic states. Indeed, psychotherapy is most efficaciously applied when the problems are in the personality only, that is, before the problems appear in the form of organic symptoms.

## 2. CYCLOID PERSONALITY

While it is valuable to divide personalities into categories, it should be realized that nature is not as strict as man is. Generally an individual is preponderantly, but not exclusively, of one type or another. Hence, in the examination and treatment of a given patient, we should be thoroughly familiar with the remaining categories.

The cycloid personality in one of his phases is characterized by *extra-ersion*, by a tendency to combine his interests inordinately in other people and other things. *He is the kind of person who subordinates his inner life to environmental needs.* It is said that he "flees into reality." He works long hours, has many irons in the fire, is full of optimism and enthusiasm, and is ever ready to talk about his projects. He usually has a great desire to get to the top, even his play carries the stamp of work and ambition. He often shows what is called a "holiday" or a "Sunday" neurosis by which is meant that, when he finds himself idle and relaxed, he promptly prepares to be busy with something.

There is a meaning behind his incessant activity, a meaning that often spells trouble. Why does this fellow have an insatiable need to absorb so much of the environment within himself? Why does he not relax and from time to time look to his inner self? Why is he so busy covering himself up with a thick career blanket? His *persona* is clearly a mask and much to his distress he knows it whenever he takes a moment off for reflection.

The trouble with this person lies in the consideration that he is constantly covering up his inner self with a welter of impersonal activities. His inner self is not allowed free and easy access to the environment. A short peep and then it is pushed back by work a-day.

problems This denial of adequate outlet for the qualities of human nature may be sustained for a long time, but it usually leads to great unhappiness, if not to a formal mental disorder (viz, manic-depressive psychosis)

Those who are close to such a person usually describe him as both a very capable man in business and, at the same time, a boy, he is mature and immature, mature in his career, immature in his emotions When his friends compel him to relinquish work for play, he is abashed and almost helpless, unless the play is childish, under which circumstances, he may be the life of the party He is the type of person who never had a childhood or adolescence, save in a perfunctory sort of way A whole block of his life has been taken out, or, better, was never lived through He went from early childhood to maturity Nature avoids, or tries to avoid, a mental vacuum as well as a physical one That is the reason why these people are usually unhappy That is the reason why, when they develop a frank maniacal attack, they live out extravagantly all and more that they had missed in former years

The cycloid personality in his other phase, and usually there is another one, gradually gives up his great output of energy, his boundless enthusiasm, his friendliness to their opposites, namely, to inertia, pessimism and seclusion He counts his past accomplishments as failures because they were performed automatically, he tells you that they were simply intellectual deeds, that only his head, not his heart was in them He emphasizes the futility of his past and he is right, for was he not an automaton, who substituted a career for wholesome living? He is dogged by his alleged inadequacies In this depressive stage his feelings of inferiority stand out in bold relief and he realizes how little he is a part of the human world around him

In the phase of depression the emotions, which formerly were externalized, are now internalized, they overwhelm him, spread throughout his body, giving rise to all manner of physical complaints It is as though the emotions stopped all his physiology, save that necessary for the minimal maintenance of life In no other clinical state is the psychosomatic relationship more widespread, more hampering The emotions blanket the body as sand does a fire

**Treatment of the Cycloid Personality**—There are many relatively mild states of cycloidism, many persons who shift from phases of happiness to those of depression When the stages are severe, leading to the diagnosis of manic-depressive psychosis, the illness should be treated by a psychiatrist But the milder states of cycloidism are usually first seen by other physicians and again, as in schizoidism, the patient presents the organic manifestations of his troubles And, again, no organic etiology is detectable Seldom does the subject ever appear

before the doctor while in the up-swing stage, because then he is confident and sure of himself and physically he feels perfectly fit.

Treatment of the individual in the depressive state is both somatic and psychic, with greater emphasis on the latter. All available measures for good physical hygiene should be instituted in order to combat the deleterious influences that the emotions are playing upon the body. The physical measures necessary to maintain some semblance of health are well known to the physician.

Psychotherapy should be promptly instituted. In the beginning *persuasion* and *assurance* are highly desirable, for the patient needs to be considerably supported mentally. He is like a lame person—hurt by walking, afraid to take the next step. He should not be encouraged to take complete rest first, because rest only gives him more time to bemoan his lot in life, and, second, because some constructive activity, however meager, buttresses his morale. Keep him going with activity commensurate with his capacities.

The patient needs someone to lean on, someone to whom he can relate his troubles, someone to whom he can transfer his feelings. If the depression is mild, the assurance type of therapy does not have to be kept up long. The physician might begin to use the more fundamental treatment, namely that which is designed to remove the cause of the illness. Assurance is merely treatment of the symptoms. Deep psychotherapy aims at the cause.

The purpose of *deep psychotherapy*, as practiced by the nonspecialist, is to make an extensive inventory of the patient's life, past and present. That is done directly through the patient, who gains emotional outlet and insight into himself while reviewing his life. By this means emotions are drawn away from the body, as they are being drawn away, they should be redirected upon natural environmental interests. The best technic on the part of the physician is to be a good and interested listener and a judicious adviser. In psychotherapy the patient does most of the work. Let him assume and maintain leadership in the interviews. The physician should be like the pilot who turns over the controls to the trainee. To do this properly takes much training and experience, for in all other treatment procedures, the physician is conditioned to taking over full control and the patient is accustomed to follow. *The traditional patient-physician relationship is reversed in psychotherapy.* This arrangement does not by any means negate the physician's influence; on the contrary, it enhances it. He becomes the trainer rather than the pilot. When he tries too much to be both, his student does not learn. Let the student observe and interpret the several dials on the instrument panel, correct him when he is in error.

Gradually the patient will see what he previously had not seen; he had not seen it because he did not want to, and he did not know how.

to see himself as others saw him. He will steadily find out how blindly he had been going through life, how blind he was to his faulty ways, how, without knowing it, he was driving furiously ahead without regard to warning signals. He will soon know how dangerously he negotiated a certain curve, merrily on two wheels, without taking his foot off the accelerator. He will soon know that he should not have driven steadily for eight hours, but that he should have stopped for refreshments and relaxation after each few hours. He will understand that he should not have bragged about the great speed he made over a long course. It was that kind of driving that eventually wore out the driver and the car prematurely.

Then, when he has seen himself, he is prepared to slow down to reasonable speed. The slowing down is not easily done, but with time and experience he will like it far better than he liked the dangerous way. He will not take rest and recreational periods easily at first, because he was gauged to speed and ambition, but when he learns that the pleasures of relaxation with people are at least equal to the pleasures of stiff, professional competition, he will wish to experience both.

He will believe you when you say, "Don't build a palace on quicksand."

### 3 HYSTEROID PERSONALITY

Some people are always in groups though not a part of them. They are lonely mixers, unless they can cause the interests of the group to be essentially converged upon them. They contact reality richly so long as reality focuses its attention upon them. They are perennial children always seeking the admiration of the parents. To them the people of the world are divided into two groups, mothers and fathers. They are greatly pleased with adulation, though they may not have earned it through any meritorious accomplishment. They are as proud over a comment made on the neatness of their appearance as they were when the family admired their first party dress. That is natural, you will say, but it is the *incessant bid for attention* that stamps the reaction as anomalous.

The hysteroid person shows very facile emotions. Laughter, tears, anger appear with ease and are usually occasioned by the attitude of others toward the subject. It is easy for him (though hysteroidism is preponderant among females) to sympathize with others, often to the extent of acting genuinely like another. He is oversuggestible. Indeed, a major fault with him is that he can far more readily be another than he can be himself. He is a play-actor, so to say, and in this respect he can often simulate, without knowing it, the physical ailments of another. This is especially true when his selfishness is punctured. Like a child who has learned the value of sickness, real or feigned, he can and does resort to it, when other means of gaining attention fail.

Not infrequently the sickness, unconsciously determined, is used as a weapon to make another fall in line with the hysteroid's interests. A verbally kind wife may punish her husband severely through the guise of illness. Through the simple expediency of physical complaints, she can control him, even make him feel like a reprobate, when otherwise she is small and ineffectual. In fact, the household may be rendered turbulent by her shifts from strength to weakness.

The chapter on the hysteroid personality is too long to relate, but the important feature here is *the facility with which physical complaints are derived from unhappiness*. This group probably makes up a fairly high percentage of the practice of medicine.

**Treatment of the Hysteroid Personality**—Treatment by *psychotherapy* is the procedure of choice. Suggestion, mild or hypnotic, works well temporarily, but the more substantial form of treatment, the kind that aims toward correcting the personality defects, is that outlined under the heading "Cycloid Personality." After all, psychotherapy is not different in kind; it is different only in the manner of application, as regards the various types of personality. Different clinical syndromes are best looked upon today as special ways of reacting to essentially similar life experiences. This is not to overlook the details that have gone into a given life, but it is a way of saying that the general framework is not too dissimilar for humans as a whole.

#### 4. COMPULSIVE OBSESSIVE PERSONALITY

Under this heading are grouped those individuals whose life is unduly concerned with thoughts and acts which are irresistible. Some people are compelled by *inner urges* to think certain thoughts that are disagreeable to them or to act contrary to their will. They may not exhibit formal symptoms, but their pattern of living outwardly conventional is rigid, compulsive, repetitious. The individual may never come to anyone's attention, particularly after he has learned how to manage the environment to conform with his ways of doing things. But when he has to conform to the demands of others, he may become petulant, irritable, uneasy. He objects strenuously to a break in his habit patterns; in fact, if the pressure brought to bear upon him is beyond his control, the compulsive features are strengthened and his energies go over to the compulsions and away from the realities of life.

These are the individuals who know that their physical complaints are due to mental tension and as a rule they do not go to the physician primarily for physical reasons. They openly state that they are beset with peculiar mental impulses and they seek treatment not for the secondary physical troubles.

Individuals who are beset with *phobias* are also having a compulsive-obsessive syndrome. Since our concern is with the somatic aspects of mental problems, no

given to those phobias that are environmentally expressed, such as fear of open or closed or high places, or the fear of animals, contamination, or needles. Rather, we shall mention only those morbid fears that are identified with organs of the body, such as fear of choking, or skin lesions.

More frequently than not these conditions are first seen by the family physician, moreover, they are seen by him before they have come fully developed or fixed. It is then that psychotherapy may be most beneficially exerted. It is generally futile to try to convince a patient of the irrationality of his fear, in fact, he knows that before he goes to the physician. What he desires to be rid of is the irrationality and that can be accomplished only by that form of psychotherapy that goes into the past life of the patient, particularly that part of his past dealing with the relationship between him and his parents.

## 5 NEURASTHENOID PERSONALITY

The line of demarcation between the neurasthenoid and the neurotic individual is an academic one. The chief symptoms are mental and physical fatigue, tension, various physical complaints and sadness. Closely related to neurasthenia is hypochondriasis, a condition characterized by prolonged preoccupation with one's health, by "innumerable" ailments of one kind or another. Psychiatrists understand the psychopathology of these states very well, but treatment is especially difficult, if not impossible, in most instances.

## IV PSYCHOTHERAPY FOR THE PRACTITIONER THE TANGIBILITY OF THE EMOTIONS

It is sometimes suggested that psychotherapy deals with intangibles; that there is nothing to put the finger on, that it is unreal. Others, believing themselves to be more charitable, speak of it as something signed for, and understood by, the specially trained alone. To hold the opinion that psychotherapy works with intangibles is the equivalent of saying that the *grief of bereavement* is intangible, when in fact the loss of a loved one induces the most tangible anxiety, the most palpable feeling of hopelessness, as touchable, in its way as the loss of one's material wealth. Length is measured with a rod, liquids with a receptacle, temperature with a thermometer, speed with a speedometer, strength with a dynamometer, grief with the heart and head. The depth of a heartache is fathomable, real, true. Grief is so tangible, indeed, that it can be recognized at a distance, it can be felt emotionally by the subject and by those about him. It is so influential that the activities of an entire household may be appreciably altered by it; it can incapacitate a brilliant mind and a healthy body as surely as a physical accident or disease can. Of course, it is tangible, very tangible.

indeed Those who are beset with grief say they would far prefer an organic sickness

Is *fear* intangible? Is the fear of failure something that does not touch us, that does not worry us sometimes to the point of creating real physical symptoms, such as loss of appetite, of sleep, avoidance of our usual associates, difficulty in thinking, not to mention a host of other symptoms Does not fear of failure often disrupt the relationships with members of a family, does it not frequently lead to economic distress? Fear is often painfully tangible Surely you can put your finger on it, but you need a different kind of a finger, a mental finger, by which you can palpate a fear as certainly as you can palpate a pulse

Is *irritability* intangible? Ask the wife whose husband is "fed up with her" whose husband neglects her for others, whose husband criticizes her sharply for no reasonable causes at all, whose husband complains about the preparation of the meals the time she spends in her boudoir, the "silly" questions she asks while he is reading his newspaper She will tell you what such irritability does to her strength, that it makes her weak, so that she can hardly do her housework or marketing, the whole body feels weary, the vitality is gone, she can hardly drag herself around She does not eat, she just puts food in her mouth, she does not sleep she merely lies down The complexion becomes sallow undernourished, pimples appear get infected Does not the gastro intestinal tract also reflect the impoverishment? On what basis shall we explain the nausea, perhaps vomiting also the sense of emptiness, if not pain in the stomach, the constipation?

Emotions are very tangible. They have to be to cause such tangible changes in the physiology of the body No wonder the symptoms persist in spite of the skills of organic medicine. Physical medicine in these instances, only touches the results, not the causes. It was a most challenging case you say but one that finally responded favorably after a year of treatment Why did the patient get better? Because her husband began to have a sense of guilt over his damnable treatment of her, underneath it all he knew why she was sick, he even suspected that he was the indirect cause of her appendicitis for which she had to have an operation Besides, he was not very successful as a philanthropist Slowly he began to appreciate his wife slowly her health was restored The intangibles were the cogent remedies The intangibles made her body well as they had made it sick

It is commonly known to all that the mind can and does 'go What is not so well known but what is equally as true is that ' also can and does 'go crazy " I don't like the term 'crazy " a definite place in the popular mind The man in the street enough does know that the body can go crazy Doesn't he has butterflies in his stomach that he has the jitters, a nervous

that his stomach is turning somersaults, that his heart is in his mouth, there's a lump in his throat, a disagreeable situation produces a bad taste in his mouth or makes him feel nauseous, the heart is broken, he is stunned to speechlessness. The distal end of the alimentary tract is also the object of many emotional comments.

These examples of body craziness are but mild symptoms of emotional disorder. The many varieties of hypochondriasis are of the same order, though of greater intensity and more disabling.

It cannot be maintained that the elements with which psychotherapy deals are intangible. Anxieties, fears, obsessions, compulsions, and the bodily expression of emotions are real and manageable.

### ESSENTIALS OF PSYCHOTHERAPY

For purposes of treatment we may arbitrarily divide clinical syndromes in two large groups, the first comprises those patients who can be adequately treated by the nonspecialist in psychiatry, the second constitutes those patients whom only a specialist should treat. Elsewhere in this issue (see "The Person in the Body") we have outlined the kinds of syndromes that can be managed by the nonspecialist.

**I. Mental Hygiene Equipment**—Our current topic deals more or less strictly with psychotherapy by the physician in his office. One might expect that the first recommendation would take the form of reading material, yet if that were the arrangement of presentation, it might tend to obscure the most important mental hygiene tool, namely, you, your emotional equipment, your life experiences and what those experiences have made of you. The reason why you acquire foremost importance lies in the consideration that in any form of psychotherapy the emotions of the physician and the patient are paramount. Therefore, look to yourself first. It would not be a bad idea to inventory yourself, to appraise your assets and liabilities, to survey your opinions of yourself and of others, to know what your philosophy of living is like. Those are some of the topics that you are going to work on in your patients, and unless you know where you stand on such matters you can hardly be expected to be impartial in the treatment of your patients.

Books and other reading material are invaluable guides, but in the long run you, not a book, are going to influence the life of the patient before you. There are many valuable books, but if I had to name a few for the busy practitioner, I would suggest the following:

*The Human Mind*, by K. A. Menninger, 2nd ed. Alfred A. Knopf, New York, 1937.

I suggest this book for two purposes, first, because it may be read to give us better insight into our own selves and second, because it will give us good understanding of the patient's mind.



*Psychosomatic Medicine*, by E. Weiss and O. S. English. W. B. Saunders Company, Philadelphia and London, 1943

This is invaluable reading on the question of the man who has the disease and the disease who has the man.

*Facts and Theories of Psychoanalysis*, by Ives Hendrick, 2nd ed. Alfred A. Knopf, New York, 1939

This is a sound and readable treatise on psychotherapy

*The Social Component in Medical Care*, by J. Thornton and M. S. Knauth. Columbia University Press, New York, 1937

This book is an intensive study of the social background of illness.

2. **Selection of Patients**—The suggestions contained in this communication are built around the thought that the practitioner may wish to treat psychotherapeutically many patients who show anomalous personality growth as well as those whose mental symptoms appear as physical complaints. The concepts refer particularly to mental hygiene rather than to psychiatry, although it is recognized that such a division is actually arbitrary. Perhaps it would be better to say that these notes have reference to both early and mild syndromes and not to advanced stages. Therefore the practitioner may apply the method to patients of any age and of any clinical syndrome. After all, the human mind in its general plan does not vary remarkably from one person to another, that is, the skeletal framework is common to the race. Variations are largely due to the strength of the framework as well as of the walls of the structure and the equipment of the rooms.

3. **Privacy**—The patient beset with an emotional disorder needs privacy. He should be advised from the outset that what he says will be kept in strict confidence and that his case will not be discussed with anyone—mother, father, wife or others—without his full knowledge and consent and only when it is believed that the imparting of information will benefit the parties involved. Unless such confidence is established and maintained the patient will undoubtedly withhold much valuable information.

4. **Duration of Treatment**—When psychotherapy is once under way the patient should be told to allow approximately a half hour for each session. The specialist allows an hour. Depending upon the needs peculiar to the given patient it may be advisable to see the patient daily or every other day, but whatever routine is established should be regularly maintained until the progress of the patient's condition calls for a change.

It is well not to set an over-all time limit. Some patients get over their immediate symptoms within a month, others may not clear up for several months. It is helpful to tell the patient that usually there are two phases to treatment, the first constituting treatment of the symptom, the second comprising treatment of the cause. Among the latter it may be mentioned are environmental situations, such as an unhappy

household, a dominating or an oversolicitous parent. Or the causes may be within the patient himself, perhaps in the form of excessive shyness or boldness. The main point here is that two parts of his life have to be treated, first, his symptoms and, second, the groundwork whence the symptoms arose. Not infrequently, indeed, more often than not, treatment of the fundamental cause consumes a much longer period than treatment of the effects or symptoms. It would be gratifying if substantial results could be achieved simply by removing the cause or causes, but experience shows that both cause and effect must be treated.

5 **Go Slowly!**—Psychotherapy should be done leisurely. Neither the physician nor the patient should be in a hurry. Indeed, a leisurely attitude, reinforced by sincere interest, commonly expedites therapy, whereas speed slows it up. Don't be discouraged, if in a given session, little seems to have been accomplished. A relatively silent session may be more valuable than a verbose one.

Impatience to get to a point may be the surest guarantee that you won't get there. If gentle urging does not help, let the topic rest until the patient is prepared to resume it.

Be a receiver of information, not a dispenser. This does not mean that you are not to counsel and advise, that you are not to judge, but it does definitely mean that if you give more than you receive, or if you give on the basis of scanty information, in all likelihood treatment will benefit you more than it does the patient. If you give injudiciously, then you give on the basis of your life history, not his. In other words, you are being treated, not he. Physicians are so in the habit of dispensing that they may forget that *in psychotherapy it is the patient who should dispense*, for the aim of psychotherapy is to drain off, with understanding, the pent-up emotions that have given rise to trouble. Draining your gall (bladder) won't help his cholecystitis.

6 **General Method of Psychotherapy**—What you are trying to do is to remove infected ideas and emotions from the body and mind of the patient. Your personality is the scalpel, your personality is the gauze by which the pus is drained to the outside. The specialist calls this by a special name, *transference*, by which is meant that the physician becomes the object of the patient's emotions, the kind ones and the unkind ones. The physician is the gauze, so to say. His very presence is a powerful therapeutic measure. That is one reason why it was suggested that he should not be too active in psychotherapy, that he should not talk too much or without complete facts before him.

Every patient, adequately treated, lives out upon the physician both positive and negative transference. This means that the patient lives out his likes and dislikes, in so doing, he attributes to the physician what he would have attributed to his mother or father, or brother or

sister or others, if he had not been repressed. The physician loses his identity as such, and is regarded by the patient as someone who means or has meant something very personal to the patient. Hence, when you are praised or damned by the patient, it is well to remember that in all probability you are not praised or damned for what you are, but for the scapegoat role into which the patient puts you. If you warrant praise or condemnation take it gently, for either is relatively unimportant to the central issues.

But emotional and ideational catharsis—catharsis in the sense of natural purgation—is only a preliminary step. Blowing off steam merely reduces pressure in the boiler by getting rid of the excess, which then vanishes into thin air. It is in the interest of economy to use the steam for the purpose for which it is intended. This can be accomplished, if we may go back now to psychotherapeutic concepts, by assisting the patient in examining the *meaning* of the ideas and emotions he expresses. What significance do the ideas possess? A patient relates that he has never been able to fall in love with a girl eligible to marry him. He covers this part of his love life in much detail. His girl friends have usually been much older than he; many of them are married and have a family. Those are the girls he likes, the kind who have a family. He soon realizes that moreover, he does not love them as sweethearts, he likes them because they are kind to him, they make him feel like one of the family—like a brother or a son or a husband. In other words his pattern of living is his own family—his own parents and siblings, he has not grown up to be on his own, to be emotionally independent. Rather in his adult life he is simply continuing to live, in a slightly different home—as he had lived in his youth.

The foregoing is but an example of what is meant by understanding the meaning of the patient's ideas and feelings. That same patient may very well under your guidance assume the role of a son to you. As a son he may both like and dislike you; that is, he may show both a positive and a negative transference. When the patient has gained insight into the part that you and he are playing then that particular phase of treatment may lead him to grow out of the childhood role and into the adolescent.

Each phase of his life is taken up separately and is treated with insight. Usually the several phases are not taken up as one piece, so to speak, though a given topic may be the paramount theme for a considerable time.

*Don't force insight.* You may know well in advance for instance behind his selection of girl friends, unaware to familiarize the patient prematurely. It is in the interest of therapy to get as present as will thoroughly convince him, the meaning of his choice of girl friends.

had in mind when we recommended that you *let the patient take and keep the initiative*

Psychotherapy has other important aims. One of them, and a very highly important one, is what we may call the *coalescence of emotions and experiences*. Some patients relate very painful experiences, but you wouldn't know from the way the patient relates them that they are painful. It is as though the patient were recounting merely by rote. The appropriate emotions are missing from the content. A cure can never be expected when the corresponding emotions are left somewhere behind. Nor can the emotions be forced out by you; you can help the patient to bring them out by reviewing with him the facts of the experiences, but you may have to wait an appreciable period of time before he is prepared to bring the two (emotions and experiences) together.

Another common mental defense is seen when the patient, relating painful experiences, takes a tolerant attitude toward them, he justifies the experiences, that is, he rationalizes. Under this condition, too, cure is not possible. The physician must help the patient to see the true meaning to him of the experiences.

*The aim of psychotherapy from the standpoint of the nonspecialist should be restricted to the treatment of conscious material.* Many of the patients whom he sees can be cured by psychotherapy of that part of the mind known as the conscious. The unconscious, that is, the hidden part of the mind, is the province of the specialist, is the province of those who are well familiar with the structure and function of the unconscious. It is dangerous to explore this realm without skill, for it contains such elements as the castration complex, the earliest manifestations of the Oedipus complex, bisexuality, cosmic identification, rebirth and a host of phylogenetic impulses.

Special emphasis has been placed upon the management of the conscious mind of the patient in psychotherapy. Without going into detail, I should like to stress also the need to get the patient's interests bound to natural and wholesome environmental objects—friends, career, recreation, and so forth. It is often necessary to encourage the patient to establish such contacts, particularly during a procedure that makes him so introspective. What you should aim to do is to get the patient to place out in the environment the newly released emotions, so that they will not remain upon you or flow back into himself.

# PSYCHOSOMATIC PRINCIPLES AND METHODS AND THEIR CLINICAL APPLICATION

RENÉ A. SPITZ, M.D.\*

## I HISTORICAL BACKGROUND

SINCE time immemorial the cure of sickness consisted of a judicious mixture of psychic and somatic intervention. To the nineteenth century, the era of materialism and specialization belongs the questionable privilege of separating the two and of neatly docketing each in a separate file. It was only in the beginning of the twentieth century that open minded clinicians began to realize the immense loss in curative effectiveness in which this separation had resulted. Curiously enough, or perhaps understandably enough, this dawning insight was paralleled by an absolutely fanatical drive to split up and segregate from each other the medical specialties on the flimsiest excuse.

Whether our new insight may lead again to a better balanced medical training and consequently to a better balanced approach to the problem of cure the future will show. There are many signs which make such an outcome probable. For the present, the result has been to invoke the cooperation of the psychiatrist in a number of diseases which were considered purely somatic only a few decades ago. With this psychosomatic medicine came into being.

The names of its pioneers and precursors are familiar enough. I read \* Bergmann<sup>1</sup> and Cannon<sup>2</sup> laid the foundations on which we have been building in the last fifteen to twenty years. A rising tide of literature on the most varied psychosomatic conditions has been published by psychoanalytically minded psychiatrists, by the more discerning clinicians among medical men, by physiologists interested in psychology and by psychologists aware of physiology.

## II PRINCIPLES OF PSYCHOSOMATIC MEDICINE

When one reads this literature one is struck by the discrepancy between the richness of the clinical material offered and the lack of a uniform direction in the theoretical elaboration of this material. This goes so far that it would not be difficult to show two articles on one and the same subject which come to diametrically opposed conclusions, both in regard to the etiology and in regard to treatment of the condition investigated. One somehow gets the idea that there must be something lacking in the method of approach in psychosomatic medi-

cine, that some of the fundamental concepts used in this approach have not been sufficiently clarified

This impression is borne out whenever one hears discussions on the subject of what constitutes psychosomatic conditions, in which the discussants very frequently agree to present their clinical material, but to refrain from defining the term "psychosomatic." Many of the older and the more recent publications on the subject illustrate this attitude. Perturbed by the logical difficulties of psychophysical parallelism, some authors declare that there is no sense in making any distinction between "psychic" and "somatic", that making such a distinction is a residual from a period in which body and soul were distinguished from each other for religious reasons. Such a somewhat dictatorial pronouncement cuts the discussion short by begging the question. This can hardly be called answering an age-old problem of human thinking.

#### PSYCHE AND SOMA A METHODOLOGICAL PROBLEM

Without attempting to solve this problem, I wish for the sake of clarity to state my position in regard to two of its aspects, the factual point of view (which could also be called the biological one), and the methodological point of view (which could also be called that of semantics).

*Factual viewpoint* Psyche and soma are biologically one, there is no division between them.

*Methodological viewpoint* Psyche and soma can be described only with the help of two different sets of semantic concepts. These semantic concepts fit into two different models of thought. The somatic model is that of cause and effect. The psychological model is that of motive and action.

It follows from this statement that the factual and the methodological viewpoints are two aspects of the same logical *problem*. On the other hand, "psychic" and "somatic" are two aspects of one and the same *biological happening*. In the present work it is unnecessary to revert again and again to the factual aspect. This is understood as our premise and accepted as such. Therefore, we will operate with the help of the methodological duality. A given phenomenon will be considered either with the help of the somatic model or with that of the psychological model according to the aspect under investigation.

It would be just as misleading to speak of schizophrenia as a somatic disease because of its numerous somatic manifestations, as it would be ludicrous to call pregnancy a psychogenic condition because of the etiological role of psychological factors in impregnation and gestation. But we would stultify our effort toward a better insight into these conditions, were we to ignore the different approaches offered by the two aspects, psyche and soma. I will, later on, show that at certain levels of evolution the distinction between psyche and soma ceases.

## CONCEPTS OF PSYCHOSOMATIC MEDICINE

So much for the basic principles of psychosomatics. Before discussing methods in detail, we will have to redefine our concepts. The somatic ones do not need redefinition since they are sufficiently well known and uncontroversial.

This is not true of the psychiatric concepts with which we have to operate. Psychosomatics have been made possible by a dynamic theory of the psyche, based on the psychoanalytic theory. It is only natural therefore that every attempt to understand psychosomatic conditions has been made with the aid of psychoanalytic concepts.

**The Unpredictability of Results.**—On the whole the results of this approach have been gratifying. We have achieved an increasing measure of understanding of psychogenic factors in diseases which up to very recent years we had been accustomed to consider purely somatic, yet in which somatic intervention had achieved disappointing, or at best, indifferent results. Our new psychiatric approach has enabled us to improve treatment at least to the extent of making life more bearable for the patient and the patient's surroundings, often to the extent of freeing the patient from his suffering. It is disturbing that these results are rather erratic and unpredictable. A psychiatrist may achieve excellent results in a series of cases only to meet with complete failure in other cases of the same description. A method will work in one case and not in another similar one. Cases involving very different organ systems will yield apparently similar etiological factors. It would seem that the approach is the right one, that we are on the right way, but that our understanding is inadequate.

We must therefore reconsider our method of approach both regarding our concepts and regarding the peculiarities of the diseases we have undertaken to treat.

**Emotional Components in Hysterical Symptoms.**—Verbal communications, the end results of underlying psychic processes, were the material on which psychoanalysis based its concepts. Psychogenic symptoms became translatable into words if one applied to them the psychoanalytic method. Alexander<sup>1</sup> quoting Freud<sup>2</sup> remarks that hysterical symptoms are symbols of a violent emotion.

The following example illustrates Alexander's statement. A married woman, aged twenty-two years, came to me with the <sup>1</sup>int <sub>er</sub> vaginismus. No somatic cause could be found for the <sup>1</sup>int which would appear in any situation which could lead to intercourse. We are justified in assuming a <sup>1</sup>int course because of an unconscious moral conflict. Since she desired intercourse, the somatic symptom which made intercourse impossible represented in particular phenomena the unconscious thought <sup>1</sup>int intercourse! Psychoanalytic intervention enabled

late the unconscious motive into a verbalized conscious one and the symptom was thereby relieved

We owe to Alexander<sup>1</sup> the insight that it is otherwise with psychosomatic symptoms. They are not symbols, they do not express an emotion, they are the physiological accompaniment of constant or periodically recurrent emotional states

In conversion hysteria we have the direct translation of a thought-content into a symbolic body-language. The causal connection is obvious and understandable in terms of our adult verbal thinking. Alexander by his definition has added to our straight dictionary translation of symbolic symptoms a set of new points of reference. We could speak of these new points of reference metaphorically as of a grammar which has been added to our symbol dictionary. The rules of this grammar are the physiological processes. Yet though this interpolation is helpful at this point, from what we have observed in cases of gastrointestinal diseases it is not sufficient

**Relationship Between Different Emotions and Their Concomitant Physiologic Processes**—It is evident that the state of things described by Alexander<sup>1 3</sup> no longer fits into the frame of psychoanalytic concepts and that we will have to add something to them. Alexander does so by introducing an unknown quantity, the relationship between different emotions and their concomitant physiological processes. He does not supply a method for determining these relations. We believe that the reason why Alexander has not filled this gap is because he has overlooked, as do many psychoanalysts and psychiatrists, the fact that the frontiers of psychoanalysis are determined by its method. The method of psychoanalysis is free association which presupposes the use of language. Any statement made by the psychoanalytic theory in regard to the period before the acquisition of speech is achieved with the help of extrapolation. But it is just the preverbal stage of infantile development which we hold largely responsible for the creation of a disposition leading to later psychosomatic disease

**Psychosomatic Conditions in the Preverbal Stage**—A series of experiments and observations have been conducted therefore by two members of the Child Research Committee of the New York Psychoanalytic Institute (R. A. Spitz, M.D., and K. M. Wolf, Ph.D.) They proved that approximately during the first three months of life there exists a period in which a distinction between soma and psyche in the adult sense of the terms is nonexistent. Undoubtedly affects are present, but they cannot be classified. They are expressed as much by affective behavior as by bodily symptoms. To put it differently. We are confronted with an undifferentiated whole, the human being, the manifestations of which show simultaneously affective and somatic phenomena

An example will explain this better than further theoretic discussion.



Timmy, a white male infant of one month and twenty-seven days, was getting an exaggerated amount of attention both from his father and his mother. If someone was in the room he screamed until he was picked up. If both parents left the room he immediately began screaming and produced abdominal spasms which were so violent that they could readily be palpated through the abdominal wall. The spasms were not accompanied by diarrhea or by constipation, and were relieved either by rocking or by a special form of massage or an equally special form of cuddling.

One cannot speak in the case of this infant of an affect which caused the spasm, not of the spasm which caused an affect. Such terms as discontent, anxiety, rage, longing, would all be inappropriate. This infant simply reacts to a situation with a response which on the one hand is an undifferentiated affect, on the other an intestinal process. If we wish to modify his whole psychic and somatic behavior the pathogenic situation has to be replaced by a new specific situation.

The example we have given is not the only psychosomatic condition to be found at this early age. There are numerous other ones which are familiar to every pediatrician. Less well known are some very early conditions appearing immediately after birth. Ribble<sup>14</sup> has described one of them. The reason why pediatricians are not familiar with these conditions is that up to two weeks of age neonates are under the care of the obstetrician who is neither pediatrically nor psychiatrically interested.

**These Early Emotional Outbursts as a Source of Later Psychosomatic Ailments of the Gastro-intestinal Tract.**—It will be seen from this that a vast field of work awaits the psychiatrist who turns his attention to the preverbal stage. For psychosomatic purposes it is necessary to stress that the gastro-intestinal tract is more closely linked to the mother and her manipulations during the first two years of infantile life than other parts of the somatic system. From the first day the mother is in constant contact with the baby's gastro-intestinal functions from its feeding to its toileting. It is around these functions that the life of the baby is exclusively centered during the first three months. It acquires other interests only little by little in the course of its first two years. We believe that we are justified in our assumption that psychosomatic ailments of the gastro-intestinal system probably have their etiological background in this early period of life, for which psychoanalytic concepts have been formed on the basis of pure construction and terms of experience. If we accept the psychoanalytic theory, predominant role of the oral zone in infants and of the early onset of anal activity (and it has been borne out by all experimental observations) we must recognize that later involvement of the gastro-intestinal tract must be understood in the term prior to this early period.

Cardiac, vasomotor and inner secretory functions have never become part of conscious processes. Their connection with the affects remains on the whole pretty close to the original model of early infancy, since no environmental pressure is brought to bear which would enforce their translation into terms of conscious verbalized thought.

### III METHODS OF PSYCHOSOMATIC MEDICINE

Since these are the main fields of psychosomatic diseases, it follows that it would be an error to approach these diseases by trying to translate them into the terms of affects. The most we could do is to postulate the simultaneous presence of certain affects which are the concomitants of physiological phenomena. But these affects vary a good deal and it becomes necessary to differentiate between two roles played by affects in psychosomatic diseases.

- 1 Affects which participate in the etiology of conditions developing often many years later
- 2 Affects appearing in these later conditions as a secondary elaboration

Our present approach to psychosomatic conditions is to try to draw conclusions from these secondary affects to the primary ones. This is a questionable procedure at best. It cannot be subjected to any form of verification, and it will always remain hazardous guesswork to be performed successfully only through sheer intuition.

How then are we to find the etiology of psychosomatic processes? We have two possible ways of approach.

1 *The Statistical Approach*—We know that environmental influences both in the affective and in the somatic field vary in different cultures. One culture may encourage or repress affects in infants, facilitate or inhibit somatic behavior patterns, which another culture either treats in an opposite manner or completely differently. Furthermore, we know that psychosomatic diseases of adults show wide variations from culture to culture. Examples for this are so familiar that they need hardly be quoted. It is a well established fact that hypertension is very rare in Negroes. Every medical man is familiar with the sex-linked differences of certain diseases in our own culture. Changes in infantile environment bring with them changes of psychosomatic conditions. Later on we will cite as examples of such change the alteration seen in the traumatic neuroses, in the psychosomatic conditions of soldier's heart and in the incidence of stomach ulcers in this war as compared to the last.

This statistical approach is promising, as may be seen, it should yield a large variety of combinations of etiological factors capable of producing a large variety of psychosomatic pictures. Its shortcoming is that it involves a huge amount of research necessitating the collaboration of ethnologists, sociologists, psychoanalysts, psychiatrists and med-

ical men. An attempt at classifying affects and behavior patterns will have to be made and as yet no Linné has been found for this purpose.

2 The Genetic Approach.—As has already been mentioned, little attention has been paid to psychosomatic conditions in infants up to now. Enlightened pediatricians have begun to work in this field and we may hope that obstetricians will join them in a not too distant future. We will then have data of the prenatal, the neonatal and the infant stages. This approach seems to be more limited in its scope, yet at the same time its promise is more immediate. Situations conducive to psychosomatic conditions will become observable, be classified and catalogued. But this will not be done in terms of affects, but in terms of situations correlated to behavior and somatic manifestations.

Such a description in terms of situations correlated to behavior patterns and somatic manifestations would give us a new set of concepts which would be neither somatic nor psychic, but would partake of both and would therefore really deserve the name of psychosomatic. It could be called a situational behavior language. We call it a situational behavior language because in this method of description definite emotional and somatic behavior patterns are coordinated to definite pathogenic situations.

In the literature of experimental psychology of infants there are a few examples which approach the line of investigation we have suggested. They are papers by M. E. Fries,<sup>10, 11</sup> H. M. Halverson<sup>12, 13</sup> and M. A. Ribble.<sup>14</sup>

A really effective presentation of this behavior language would have to be made with the help of vectorial diagrams. Such a set of diagrams, combined with the case histories of the infants in question, have been worked out by two members of the Child Research Committee of the New York Psychoanalytic Institute, R. A. Spitz, M.D., and K. M. Wolf, Ph.D.<sup>15</sup> I regret that in the space at my disposal I cannot present them. They will be published in a special article.

#### IV. CLINICAL APPLICATION

Eventually both the static and the genetic methods would have to be combined. This would give us the real key to the understanding of psychosomatic diseases. Understanding, however, is not cure. In all fields of medicine cure is at first attempted and in a certain measure achieved despite inadequate understanding. No one knew what caused malaria when it was already treated with quinine. No one knew why sulfa drugs were effective, but they were already being applied.

The situation is the same in the case of psychosomatic medicine. What we know is that the patient's affects, the different aspects of the patient's personality and its relation to his environment are in the causation of these diseases. We therefore study the patient's environment and to relate

connection the sex of the therapist and his personality is nearly as important as the therapist's knowledge of psychic mechanism. A striking example of this can be seen in the treatment of ulcerative colitis where patients sometimes could be approached and cured by a male psychiatrist, sometimes by a female one and sometimes by neither, or signal improvements could be achieved by assigning a private nurse to the patient.

This intuitive approach to the problem of the cure would gain enormously if we could add to it the insight to be won through what we have previously called the *genetic method* of investigating psychosomatic conditions. If we are able to ascertain the connection between early infantile situations, behavior patterns and somatic manifestations, then it may become possible to apply a psychotherapy to the individual psychosomatic case which will be more than guesswork and intuition.

#### EXAMPLE OF STATISTICAL APPROACH

The other line along which a cure can be developed is given through the second approach, that which I have previously called the statistical method.

**Decrease in Incidence of Traumatic Neuroses in This War**—In a paper read at the psychiatric convention in Detroit on "Traumatic Neuroses" I cited<sup>15</sup> an example of this method of procedure. I took as starting point the enormous decrease in the incidence of traumatic neuroses in this war as compared with the last. I concluded from this decrease that the soldier of today has an increased resistance to psychic trauma. Since this resistance, the so-called "Reiz-Schutz," is a function of the Ego, it becomes necessary to investigate in what manner the Ego has changed in the course of one generation. Such an Ego-change could only be the result of a modification of environmental factors during childhood and adolescence, the years in which the Ego is developed and established. It could be proved that such a change in the dynamics of the environment had actually taken place. The change consisted in a more liberal attitude on the part of parents and in a decrease in overprotection of children, which went hand in hand with a habituation to the minor traumas of sports and games.

As a result of these findings I suggested, as a prophylaxis against traumatic neuroses, that exercises be instituted to desensitize inductees to trauma. On the basis of further conclusions drawn from infantile methods in recovering from trauma, it was further suggested that the cure of traumatic neuroses should begin immediately after traumatization and should take the form of a reconditioning of the Ego.

**Decrease in Incidence of "Soldier's Heart"**—A short time ago, William Dunn<sup>7</sup> published an interesting review on "Gastroduodenal Disorders: A Wartime Problem." He quoted a large number of statistical investi-

gations to show that the most prevalent form of psychosomatic diseases in the first World War was "soldier's heart" (effort syndrome). It appears that in the present war this condition has become a comparatively insignificant problem of military medicine. This finding is very surprising, particularly when we consider the fact that the somatic factors which one would expect to be responsible for a condition like soldier's heart, are infinitely more severe in this war than in the last. The effort furnished by the individual soldier in action is a very much greater one. Similarly, the anxiety and consequently the tachycardia provoking experiences in this war appear to be infinitely worse than in the last war whether they involve dive bombers, mines, tank attacks, heavy artillery, torpedo, flame throwers or the suspense when confronted with the expectation of all this.

**Increase in Gastro intestinal Disorders**—The decrease in the incidence of 'soldier's heart' becomes still more surprising when we learn that the cases of gastro intestinal diseases, ranging from dyspepsia to peptic ulcer have *increased* thirty-six fold from the last war to this one, in which they represent up to 36 per cent of all cases under treatment. This in spite of the fact that the nutrition of the soldiers of today, the care devoted to keeping them at all times well and properly fed, has been greatly improved. It seems as if the psychosomatic disease of the first World War the "soldier's heart" has today been replaced by the "soldier's stomach."

**Could a Modification in the Ego Structure Be Accountable?**—The environmental factors appear to be such that in both cases we would expect the reverse of what has happened. We would expect heart neuroses to increase and gastro-intestinal disturbances to decrease. Why has the opposite of this happened? Since it cannot be the modification of the actual environmental pathogenic factors on the battlefield nor in the service which is the cause of these variations, a change must have taken place in the subject of these diseases in the soldier himself.

Can we again refer this change to a change in the Ego? When we speak of the syndrome called "soldier's heart" the answer is probably in the affirmative. It appears to me that the conditions conducive to the development of soldier's heart are very similar to those which lead to the traumatic neuroses. Not only in its origin but also in its manifestations, soldier's heart shows some of the characteristics of the traumatic neuroses, namely a somewhat disordered medley of overflow reactions largely of the autonomic kind. Here as in the traumatic neuroses, it is the stability of the Ego structure (acquired during the pre-oedipal, oedipal and latency stages) which seems inadequate or rather as if the Ego were not sufficiently resilient. I believe that a modification of the Ego consisting in a development of better defenses and a decreased disposition to anxiety is responsible for the great decrease in the incidence of "soldier's heart."

But when we come to the problem of dyspepsia and peptic ulcer, there seems to be no likelihood of a "breakthrough" of the defense organization of the Ego. In gastro-intestinal diseases the role of Ego defenses against trauma coming from the environment is apparently a minor one. But can we imply that a change has taken place in the *Id*, which according to definition is mainly composed of drives? That is hardly likely. What actually did change is the relation between Ego and *Id*. The Ego, as mentioned before, has become not only more resilient, but also much better able to permit the discharge of *Id* tensions. In its capacity of that executive organ of the *Id* which controls motor function, the Ego has to regulate the discharge of *Id* tensions. It is the disturbance in the regulation of tension discharge which, from the point of view of dynamics, is at the bottom of psychosomatic conditions. Alexander<sup>3</sup> based his theory of the psychogenic background of gastro-intestinal diseases on the parallel between the malfunction of discharge mechanisms of psychic tension and that of discharge processes of physiologic tension. We believe that this principle applies probably to all or most psychosomatic conditions and certainly includes those of the cardiac, inner secretory, and vasomotor diseases which we classify as psychosomatic. If we accept Alexander's interpretation of the psychic causes of peptic ulcer, we have to assume a highly accelerated discharge of tensions in this disease. In heart conditions it is probable that the opposite is the case, that there is a retardation of discharge and a consequent rise of anxiety.

From the assumption we have made concerning a modification of Ego structure in the course of the last twenty years, it appears that the Ego structure of the present generation greatly facilitates the possibilities of discharge and, as we have just shown, accelerated discharge of tensions is one of the causes of gastro-intestinal disease.

**Frustration in the Oral Stage as a Factor in Increased Incidence of Psychosomatic Diseases of the Gastro-intestinal Tract**—There are, however, deeper reaching differences between the way the soldiers of the last and those of this war were raised in early childhood. So far we have been discussing the strengthening of the Ego and the lack of frustration in the pre-oedipal and oedipal phase. The change to which we are now referring is a change in the nursing habits to which the present generation was exposed in its infancy, compared to the nursing habits prevalent in the last generation.

The infants of about fifty years ago were mostly breast-fed and a very liberal attitude was taken in regard to their demands. When the child cried, it was given the breast. Twenty-five years ago bottle-feeding became the rage. Feeding schedules were invented and the child was fed, not when it desired it, but according to a rigid schedule invented by pediatricians more for purposes of an orderly bookkeeping

on the part of the mother than in view of the actual physiological or psychological needs of the child

It is hardly necessary to stress that such a method of feeding results in periodically recurring frustrations of the bottle-fed children. This is a frustration of the oral zone and in immediate connection with it, of the gastro-intestinal tract. Thus while the World War I generation had full gratification in the oral phase, but was frustrated during the oedipal phase, the modern generation was frustrated during the oral phase, but more liberally treated during the oedipal phase.

It is perhaps not too much to assume that a frustration in the oral stage and in the oral zone creates a disposition to psychosomatic conditions of the gastro-intestinal tract which breaks out when severe frustrating environmental conditions have to be endured simultaneously with a separation from the security of the home and the parents. This is the situation of our soldiers.

I believe that the fact that the incidence of gastro-intestinal conditions as a whole has increased in recent years by only 20 per cent in the rest of the population does not invalidate this assumption. It simply shows that the conditions creating a disposition for gastro-intestinal involvements are general in the population at large but that the psychological threat which provokes these outbreaks is more frequent in army life than in civilian life.

Some examples have been given of the practical application of psychosomatic principles and methods. It should be possible to use these principles and methods similarly in the numerous other forms of psychosomatic disease. It will probably be found that in some forms the genetic approach in others the statistical approach is the quicker and the more promising one. As the first World War proved to be one of the strongest stimuli medicine at large, and psychiatry in particular, have ever received so we can expect an increase in our experience from the present war. The first World War enriched our knowledge in the field of neuroses in particular traumatic neuroses and the treatment of psychoses. It is to be expected that the results of our experiences in this war will open novel ways of dealing with psychosomatic diseases.

#### SUMMARY

Methods and principles underlying psychosomatic medicine have been discussed. The principles have been delimited as reaching beyond our present psychoanalytic concepts and were defined as situational behavior concepts.

The application of these principles in the form of the genetic and of the statistical method was shown by means of clinical examples.

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## PSYCHOSOMATIC FACTORS IN DISORDERS OF THE CIRCULATORY SYSTEM

NOLAN D. C. LEWIS, M.D.\*

IN THE biologic organization of the body complexes there are phylogenetically and ontogenetically, two master integrating systems of organs—the nervous system and the circulatory system. While several other organs of the body are in vital positions as far as life maintenance and economy of function are concerned, the biologic activity of the organism in the aggregate depends constantly on the integrity of these two great systems.

As the mind represents the total activity of the organism, one should expect to find definite mental deviations during both structural and functional alterations of the organs of the body, and particularly in connection with those of such integrative significance as the heart and its extensions.

### EFFECT OF EMOTION UPON THE CARDIOVASCULAR SYSTEM

Emotional disturbances may directly or indirectly affect the cardiovascular system in many different ways, but it has been contended by some of the older writers that of all the functions of the body, the heart and its extensions are the least modifiable by the "will." However true this statement may be in a general way, it is a well known fact that certain individuals are either so constructed or integrated that they are able to change at least the rate of the heart beat "at will." Occasionally persons are demonstrated in the medical clinics as curiosities, who are in "conscious control" of several autonomic functions and are able by "taking thought" to reduce the pulse beat to as low as 50 pulsations per minute or to accelerate it to 120 per minute within a few moments of time. Thus according to the reports of the subjects, is usually brought about by a mental representation of certain emotional situations. While the average person cannot effect such a reaction, it reveals the presence of some psychophysiological relationship.

In the unconscious or emotionally determined cardiac disorders of everyday life there may be an otherwise important organic lesion on which an emotional fixation with unconscious phobic elaboration has formed, or there may be no objective nucleus to account for the focalizing of the disorder. Some form of fear is usually in the foreground, and the problem tends to become a complicated one. The immediate effect of acute fear on some of the physiological processes has been

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\* Present, New York State Psychiatric Institute and Hospital.

experienced by almost everyone C Macfie Campbell<sup>1</sup> has stated a part of the situation as follows "We may check our tendency to flee, but against our wishes our heart beats wildly, our respiration is modified, our tongue cleaves to the roof of our mouth, our knees knock together and barely support us and we break out into a cold sweat"

"The action of the heart in such a critical situation cannot be understood under the simple categories of internal medicine, the internist is thus confronted with the problems of the instincts and the emotions This is no unique situation in internal medicine, chorea, exophthalmic goitre, and diabetes have already brought up the same situation"

"Has the patient a special type of inferiority of the cardiovascular system, quite independent of instinctive or emotional demands, or are the cardiac symptoms altogether dependent on an unsatisfactory instinctive or emotional life, or in most cases are both factors involved—on the one hand a cardiovascular system constitutionally oversensitive or of low resistance, and on the other an instinctive or emotional life that involves a good deal of tension"

#### EFFECT OF EMOTION ON THE HEART

The heart is an organ which is highly sensitive to emotional excitement to the extent that very few individuals even claim an immunity from this susceptibility, and a long-continued period of even mild anxiety renders the organ irritable and liable to become excited under a relatively slight excess of emotional feeling The pulse of such a person may become accelerated by the simple act of taking it. Active fear and rage produce palpitation Rage may also produce precordial oppression and is known to have brought on attacks of syncope or even of angina pectoris Excessive grief may initiate a functional disorder with altered action of the valves, the patient becoming pale and anemic Many of the keen observing physicians of other days noticed that anxiety, disappointment and grief altered the heart functions and that contentment or peace of mind favored its healthy action In cardiologic as well as in other problems of internal medicine it is always well for the physician to keep in mind that all human beings possess an emotional equipment which is a part of physiologic function and which at times may dominate the whole situation, the process taking place outside the realm of conscious awareness and rational thinking

The heart may respond to emotion or excitement in one of two ways (1) Sometimes an "emotional shock" will retard the heart beat until a partial or complete *syncope* is produced While repeated syncope is not so common in organic cardiac disorders, syncopic sensations are of very frequent occurrence in the "cardiac neurosis," and many patients become "faint" whenever anything occurs of sufficient intensity to upset the emotional balance This faintness is usually ac-

accompanied by a temporary *bradycardia* (2) In the majority of emotional situations the heart rate increases in rapidity, and instances of *tachycardia* reaching 120 to 150 pulsations per minute are often noted. This may or may not be accompanied by distressing thoracic or other sensations.

Tachycardia may become an outstanding symptom in the following emotional settings:

1 It may be a continuous expression of a constant, fairly active, internal unconscious conflict, which sometimes has been satisfactorily rationalized.

2 It may obtain periodically as part expression of the memory of a former emotional situation or "shock."

3 It may become exceedingly active during "nightmares" or fright dreams, the patient awakening during the attack.

Respiratory symptoms and vasomotor phenomena often accompany emotional disturbances of the heart, and palpitations and arrhythmias are frequently expressions of tachycardia of short duration. The chief importance of these symptoms in nervous persons is that they may and usually do become foci for phobic elaborations which in turn enhance and increase the disagreeable symptoms.

#### CARDIOPHOBIA

The development of phobic symptoms in connection with the heart action is very frequently found among neurotics, because of the natural emotional irritability inherent in the adaptive motor mechanism of this organ. The heart action becomes a prey to auto and hetero suggestions of all sorts and this chiefly because of the attitude of the public toward heart disease. To the public in general "heart disease" is an hereditary condition and many individuals are obsessed by the fear of "dropping dead," particularly if there have been ancestors suffering with cardiac affections. If an ancestor has died unexpectedly from heart trouble, even in old age, the event may become a focus of fear for some of his descendants, who thus sensitized tend to interpret each transitory emotional "misbehavior" on the part of the heart as a sign that sooner or later they must succumb to "heart disease."

In keeping with the fact that phobias of hypochondriacal type often assume a faddistic turn of expression, one is reminded by history that there was a certain period when "heart attacks" were very prevalent. In the melancholy poetry of the middle of the nineteenth century it was considered the fashion if one were at all inclined to be sentimental to say that one's heart was a little disordered.

The physician is far too often the immediate cause of cardiac phobic fixations of a certain kind. Individuals with transitory palpitations or with cardiac irregularity or with some extracardiac disorder may develop a lifetime of cardiac phobias by the

cian who auscultates the chest. Often the physician makes an unusually careful examination in order to completely convince himself that nothing serious is the matter. In this situation he should make sure that the patient does not interpret this painstaking as a sign of perplexity, or that the condition is a serious one requiring an extra amount of diagnostic endeavor.

Following such an examination and the physician's final report that the condition is "not serious," will be "outgrown," is "temporary," and so forth, the nervous patient may carry away (and frequently does) the impression that the condition has been purposely minimized in order to save him fright, worry and "mental pain," an impression which may spoil his entire life, and start a "neurotic round" of visits to heart specialists. Remarks on the "negative aspects" of heart conditions such as "this could not be a mitral stenosis" or "an aortic aneurysm does not develop in this manner" made before patients are particularly dangerous as they speak for obscurity and become the source of future ruminations. The more skillful and noted the specialist the more impressive is his presence for good or ill to the patient in this respect.

While commenting upon the influence of the physician in fixing neurotic ailments on the heart, mention should be made of the more inclusive comments of the German psychiatrist Bumke,<sup>2</sup> who twenty years ago emphasized the attitude of the physician as a cause of psychic disturbances. He included this special group of disorders under the name of "iatrogenous" affections. He pointed out that a careless word about the arteries, about "hypertension," about the "heart showing a slight tendency to fatty degeneration," or similar phrases, might endanger the whole outlook of the patient. Another point was that nearly everyone has such a dread of disease that a critical attitude toward it in themselves is impossible—even a physician is unnecessarily overanxious about his physical condition, or at least about that of his wife and children (in the experience of many he is even more so than the average person).

Bumke asserted that the most outstanding excesses in masturbation cause less harm than some occasional untoward remark on the subject by a physician to those who have infrequently indulged in it. Under certain conditions "hysteria" is a dangerous diagnosis, since through the attitude of the relatives with their misconceptions of the disorder, it may produce an active antisocial attitude on the part of the patient.

Bumke described an instance in which a physician sought to tranquilize a patient suffering from a very serious disease by assuring him that certain other persons affected in a similar manner had survived as long as two years, also a man with syphilitic aortitis had lived in a happy manner until a noted internist cautioned him against the risk of going about the street alone. It was seven years before the expected

breakdown occurred but in the meantime the patient was mentally miserable and became a grave hypochondriac

Lying to patients, as such is not to be advocated, but it is not always necessary or wise to tell everything particularly those things of which we are ourselves uncertain as to the prognosis, e.g., the problems of heredity, Argyll Robertson pupil and certain heart lesions

As the heart is an organ of active motility, there are local sensations produced by its action that are normally not annoying and usually not even registered in consciousness. However a "sensitive" person may become aware of its behavior and thus become cognizant at times of a cardiac abnormality such as palpitation irregular action bradycardia and unusually forceful beats. This creates a situation of worry self-scrutiny and preoccupation which is based on the common knowledge of the relationship between heart integrity and life

Moreover cardiac phobias are frequently caused by many unrelated or remotely related symptoms, such as slightly swollen ankles from varicose vein complications sensations of vertigo ordinary dizziness from eye conditions scanty urine from physiologic reasons, and above all from "getting out of breath" whether it be from running upstairs exercising after a full meal, or purely from fear. Emotionally enhanced physiological tachycardia usually attends all of these conditions and thus the patient sees reason for attributing the previously mentioned phenomena to the rapid heart i.e., the alteration in the heart's function

Angina pectoris phobias may arise from a "stitch" in the shoulder from intercostal neuralgia or from a precordial pain from various rheumatic affections, and from arm pains particularly in those who are convinced that they are suffering from a heart lesion and who have done some inquiring comparing and reading on the subject. Vertigo tachycardia shortness of breath precordial pain and heaviness in the left arm constitute a well known neurotic syndrome but one that obviously requires skillful diagnostic differentiation from a structural disorder

#### NEUROCIRCULATORY ASTHENIA

An interesting syndrome with certain constitutional components was brought into the foreground during World War I. This disorder of the circulation was described under several different names, a few of which were 'irritable heart of soldiers,' 'disordered action of the heart' "effort syndrome" 'debility' and neurocirculatory asthenia." It was characterized mainly by irritability of the heart action and an increased susceptibility to fatigue in which no definite pathologic lesion or underlying pathologic process could be discovered to account for the reaction. Oppenheimer and Rothchild<sup>2</sup> in summing up the situation stated in effect that the "irritable heart" of soldiers was certainly not a clinical entity but that in half of the cases there were

psychoneurotic factors in the family history and other psychoneurotic predisposing elements. In about 70 per cent of the cases these authors found a history of constitutional asthenia and there always had been an irritable weakness of the innervation of the entire circulatory system. Another group seemed to be originally fairly stable but broke down under excessive strain and excitement.

These two groups probably represent examples of similar reactions in which the original focus or fixation points are on the one hand principally located in the neurovegetative integrations, and on the other hand in the personality maldevelopment where environmental situations release the disorder which has formerly been quiescent.

There is quite a wide variety of symptoms. In addition to the undue fatigue on effort, some of the common ones are excessive perspiration, palpitation, precordial pain, and a sensation of breathlessness, headaches, blurred vision, giddiness and sometimes syncope, tremors, various signs of vasomotor instability, insomnia and nightmares. Many of these symptoms are increased by physical effort, particularly the pulse rate which may be normal when the patient is at rest, but may readily become accelerated to 120 per minute or over. The heart is rarely enlarged but may show sinus arrhythmia and paroxysmal tachycardia. Short systolic murmurs are not uncommon. In most cases the roentgenographic and electrocardiographic examinations reveal nothing of importance.

#### THE "NERVOUS" OR "NEUROTIC" HEART

The term "nervous" heart as commonly used includes a number of disturbances of the efferent and afferent nerves of the heart. These are caused by several fundamentally different conditions the essential feature of which is anxiety of greater or lesser intensity. The symptoms may appear in any one of a number of recognized neurotic patterns. They may constitute a part of a neurasthenia, a hypochondria, a hysterical substitution or conversion, an anxiety neurosis as such, or they may exist chiefly as an obsessional focus. The efferent disturbances interfere with the frequency or force of the heart action, while the afferent result in an increased perception of the heart action, pain or other annoying sensations. These may be combined in the same clinical picture.

A heightened consciousness of the movement of the heart is a most prominent complaint which is often exaggerated at night. This may be enhanced by lying on the left side, or on the right side. Often there is a definite position fear and aversion. That lying position difficulties and heart consciousness in general are usually not due primarily to cardiodynamic changes is borne out by the fact that most patients with organically impaired hearts do not emphasize these complaints.

Precordial discomfort is common, being felt as a dull ache, a burning

sensation a soreness or as sharp pain. These feelings rarely have any relation to physical effort, excitement or meals. Pains may radiate to the left arm or to other regions of the body. Other symptoms are increased susceptibility to fatigue, shortness of breath, tendency to sighing, undue perspiration particularly of hands and axillae, feelings of faintness, palpitation and coolness of the extremities. Nervous heart symptoms thus include many of those of organic heart disease (Kilgore,<sup>4</sup> Caughey,<sup>5</sup> Sprague,<sup>6</sup> Miller and McLean<sup>7</sup>)

#### HEART DISORDER WITH NEUROTIC SYMPTOMS

While the majority of patients consulting the physician for symptoms referring to the heart have no objective or laboratory evidence of organic heart disease, it has often been demonstrated that a cardiovascular deficiency with its attending symptoms due to a hypoevolute (drop heart—hanging heart) condition with or without status thymico-lymphaticus features, or to an infantile nutral configuration with the right portion predominating in a fashion normal for apes, or to various acquired cardiac lesions may be associated with so-called "neurotic symptoms" which have developed in the midst of or on the basis of the existing heart condition. As the patient becomes aware of the basic disorder, states of apprehension, fear and panicky sensations alternating with mild depressions or mental irritability may develop which complicate the medical and nursing treatment. The neurotic person suffering from heart disease may increase the burden on the heart either by the constant tension caused by psychic conflicts or by means of acute emotional episodes. These emotional situations may, and often do, hasten a cardiac failure which might have been postponed, indefinitely, in the absence of the neurosis or as the result of a proper psychological treatment of the condition.

Various mental symptoms may become evident and even pronounced in the event of pain and heart failure occurring in association with angina pectoris, endocarditis, myocarditis and precordial conditions which may produce active dissociations of the personality with odd delusions based on misinterpretations of the cardiac phenomena. When there are notable disorders of the circulation such as vasomotor constrictions or feebleness of the heart's action with cyanosis, or secondary lesions in the brain such as embolism from valvular lesions or edema from incompetency, active hallucinations, confusions and disturbances in memory and judgment may appear.

While it is true that neurotic expressions and elaborations are found in connection with and superimposed upon organic heart irregularities and lesions, one should use great caution in deciding the diagnosis to actually establish the presence of a heart lesion in order to avoid putting the cart before the horse. It is probably a far more common thing that the heart's hurry and irregularity is due to an original

neurosis The "organic" part when discovered may well be of secondary development and importance, and in an outstanding number of cases heart irregularities are notoriously difficult to ascribe to a definite somatic pathology Many of these cardiac disorders of action exist throughout a long life without discoverable pathologic change, even at postmortem examination, and with or without a coexisting neurosis in some degree

From time to time physicians have emphasized the physical importance of *dreams* in heart conditions, expressing the opinion that exciting dreams, some of which may be released by gastro-intestinal disturbances, presence of food and so forth in those having cardiac disease or hypertension, may lead to acute dilatation of the heart or rupture of a cerebral artery, and thus perhaps to death from the excitement The role of the pneumogastric mechanism in dreams is self-evident, but causes and effects are here as elsewhere in this field very difficult to differentiate, as the dream in itself is usually only a symbolic expression of certain aspects of the general situation (Connor,<sup>8</sup> Yaskin,<sup>9</sup> Lewis,<sup>10</sup> Schnur<sup>11</sup>)

#### VASCULAR CONDITIONS

**Blushing**—Many besetting phobias arise from emotional interpretations of vasomotor phenomena Vasodilatation as seen in blushing is one of the most common annoyances Persons differ widely with respect to this type of vasomotor lability and in some even a slight emotion will produce a deep flushing reaction, in relation to which a marked fear may develop, the fear itself then becomes capable of initiating the dreaded reaction This erythrophobia may not be confined to the face or exposed surfaces, but may spread over the neck, chest, back, and in exceptional instances, over the entire body With many of these "sensitive" individuals social life is practically an impossibility, and "all pleasures are spoiled by a hot and burning face"

**Paleness**—There are other individuals who turn pale in emotional situations from a vasoconstriction In some instances this may become extreme, constituting an "emotional shock" with marked pallor and syncope The reaction may be initiated by any emotion such as anger, fear, surprise or embarrassment

Other phobic manifestations form about ideas concerning high blood pressure and arteriosclerosis

**Emotional Hypertension**—An emotional hypertension is a very common variety of response particularly when a sensitive patient is undergoing an examination for life insurance, or for general diagnostic purposes Under these conditions it is not an uncommon thing to discover an increase of from 20 to 50 points on the manometer Physicians should always keep this possibility in mind, since if such a patient becomes convinced or even aware of high blood pressure it serves as



a center of lively preoccupations which are highly enhanced by the popular methods of advertising of the "quack" concerns, by overworking the altruistic tendency to spread abroad medical literature for the purposes of "educating the public," and often by the advice of the local druggist. Then follows the usual round of doctors, the development of the "pulse feeling" habit, the listening for the heart beat when the ears are against the pillow at night, the consequent insomnia and the fears of presenile arteriosclerosis, and of other circulatory disorders.

**Psychic Factors in Essential Hypertension**—In recent years a number of special studies have revealed that psychic factors play an important part in essential hypertension. The individual emotional elements influencing blood pressure readings, the beneficial part rest and mental quiet play in the relief of symptoms and the aggravation of the hypertension produced by anxiety are all well known to practitioners. But in addition to these facts, according to the investigations of Hill,<sup>12</sup> Wolfe,<sup>13</sup> Menninger,<sup>14</sup> Alexander<sup>15</sup> and Saul<sup>16</sup> among others, the type of personality and the whole emotional life situation seem to constitute the setting in which this complex physically expressed disorder develops.

Patients with hypertension, while apparently friendly and self-controlled, have anxiety and strongly repressed aggressiveness beneath the surface. This repressed hostility which is denied a free natural outlet creates an extreme psychic tension expressing itself in a heightened arterial pressure. There are a number of other aspects to this picture which have been revealed and which are being investigated in several medical centers. Those physicians having special interests in the findings should consult the references appended to this article.

#### THERAPY

Patients who develop anxiety reactions are obviously in need of organized and systematic psychotherapy. Where this is not available, assurance, accurate information concerning the disorder, and suggestive therapy are helpful and often successful. Under the influence of simple explanation and assurance a high blood pressure in an emotional patient may drop 20 to 30 points in the space of a few minutes. Such a response is common in patients who go from physician to physician to have their "blood pressure taken."

In the event that there is present a severe or serious heart lesion with a superimposed neurosis, some sort of *psychotherapy* is urgently indicated since it may relieve not only the fear and emotional tension but thus indirectly aid the organic condition and prolong life. In these cases if organized psychotherapy as such is not available one can at least carry out the admirable advice of P. D. White<sup>17</sup> who states, "A part of the treatment, often of vital importance is a cheerful, firm, and

lovable attitude on the part of the nurse or physician. Such is psychotherapy whether labeled that or not, it is always an important weapon of the physician and nurse against disease. When a successful and cheerful physician holds sway there is no need for Christian Science. The ideal family physician in every generation has practiced the best of psychotherapy."

There are a number of methods or procedures used in psychotherapy. Among these are

1 **Explanation of Symptoms and Persuasion**—This has only a limited application and is unsatisfactory in the majority of cases, since it involves some conscious argument with the patient, and even when it is well managed to the extent that it removes some of the distressing symptoms, it usually leaves the basic conflict unaltered and the real causes of the trouble untouched. It goes without saying that the success of this form of psychotherapy as well as all of the others mentioned below depends upon the amount of confidence the patient has in the physician, or what has been called "transference."

2 **Systematic Organized Suggestion**—In this procedure the physician uses more active suggestion and influence. This fails also to reach the cause of the patient's conflict although it may remove symptoms. At any rate, it is more radical than just persuasion and particularly is this true of the form of suggestion which is carried out under light hypnosis. The light hypnosis may work satisfactorily in many conditions in children, in those adults who are not suitable for deeper analysis, and also for some older people.

3 **Hypnosis**—This may be used as a healing factor when directed against the symptom to be eliminated. By this method forgotten experiences are brought back to memory which effects a certain amount of "cathartic" elimination. In the hands of the expert this is a valuable method for many mental problems.

4 **Conversation Method, or Spontaneous Word Catharsis (Psychological Reeducation)**—This is a useful method of temporary, palliative treatment for some patients in the midst of urgent problems. Here it is absolutely essential that the psychotherapist have a keen insight into psychological processes, a high degree of intuition, and a unique skill in simplifying what are ordinarily more prolonged and involved technical matters. A great deal of anxiety and tension can be relieved by this type of ventilation of conflict.

5 **Organized Psychotherapy In the Form of Psychoanalysis**.—Contrary to the general impression gained by a good many people, including physicians, the aim of psychoanalysis is not to tell people unpleasant truths, but to attempt by the use of a special, and not easily acquired technic, to give to the person the use of his integrative powers in establishing a rational and conscious personality which will enable him to cope with his life situation. It is the most thorough and efficient of all

methods when applied to properly selected patients, and it lends itself to a considerable amount of modification in its application to different individuals

It should be understood that it is only by some method of deep analysis that the fundamentals, roots or actual causes of the neurosis can be removed although it may be said that favorable results attained by the other methods are sometimes permanent on the basis that the patient when free of symptoms gains mental strength and reinforces his repressions so that they do not break through again in neurotic manifestations. It should also be understood that no method is a cure-all for every neurotic disorder. Like all other conditions which come to the attention of the physician the neuroses vary in severity, in chronic manifestations, and at least in part are highly resistant to modification. Complete recoveries are often difficult to secure.

### CONCLUSION

The first concern of any individual is to continue to survive in his particular environment. Cardiovascular conditions constitute a serious threat to survival, a threat that the organism attempts to meet with all the equipment of structure and experience that it possesses. Moreover, human beings are equipped with affective or emotional mechanisms, outside the pale of conscious awareness, which are not influenced to any great extent by the "logical" thought which dominates a number of other activities. These emotional dynamic processes influence and in certain situations dominate and even determine pathologic processes to a marked degree.

Many cardiovascular nosophobias are accidental and temporary; others are based on the deeply seated needs of the personality and are thus persistent and more or less resistant to psychotherapy, while still others are of definite hypochondriacal or of constitutional significance with incurable aspects, and with the whole life dominated by a "cardiac error in thinking."

In these disorders where it is often difficult to distinguish between the presence and dominance of an organic disease which may be complicated by neurotic symptoms and a classical neurosis a careful differentiation must be attempted. However in any of these situations if the disorder reveals obvious emotional components, psychotherapy is indicated. Psychotherapy skillfully managed practically always helps as a supportive procedure even when the principal disorder is organic and requires other active medical attention.

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# NEUROCIRCULATORY ASTHENIA DUE TO SMALL HEART

COMMANDER A M MASTER\*

MEDICAL CORPS UNITED STATES NAVAL RESERVE

In a preliminary report<sup>1</sup> the importance and frequency of the "effort syndrome" or "neurocirculatory asthenia" in the armed services was emphasized. In this paper it will be shown that the cardiac symptoms and signs of this syndrome are caused by congenitally small hearts.

At the present time the effort syndrome or neurocirculatory asthenia is considered to be a psychosomatic, functional disturbance. This is

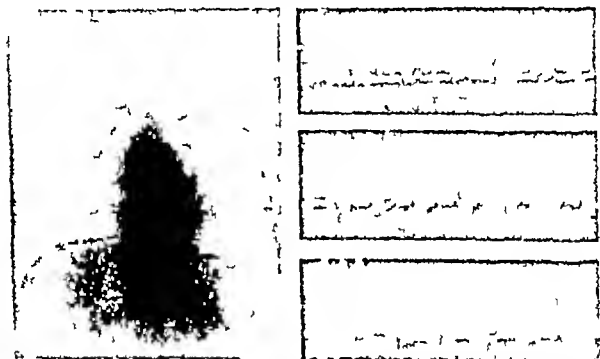


Fig. 45—R. I. S., an apprentice seaman, aged twenty-one years, U. S. Naval Hospital, Mare Island, California. Effort syndrome (neurocirculatory asthenia). Had been subject to spells of painful and rapid heart action for at least four years before his enlistment, March 2, 1941. Always nervous and tired easily when working. Teleoroentgenogram revealed a small heart. The electrocardiogram showed a small QRS<sub>1</sub> and relatively tall QRS<sub>2</sub>—RS—T<sub>2</sub>—slightly depressed. Heart rate 95 to 115 per minute.

symptoms, such as "nervousness," "shaky feeling" and "trembling," doubtless are neurogenic in origin and predominate in some cases of the effort syndrome, in the majority the chief symptoms are cardiac and may be attributed to the presence of a small heart. These include weakness or fatigue even after ordinary exertion, tachycardia, palpitation or a feeling of irregular heart beat, precordial or substernal pain, chiefly on effort, dyspnea or even orthopnea.

The concept that a heart small in relation to the body is inadequate for work was first stated by Laennec<sup>2</sup> in 1826 and recognized by Rokitsansky.<sup>3</sup> Laennec found the hypoplastic heart more common than the

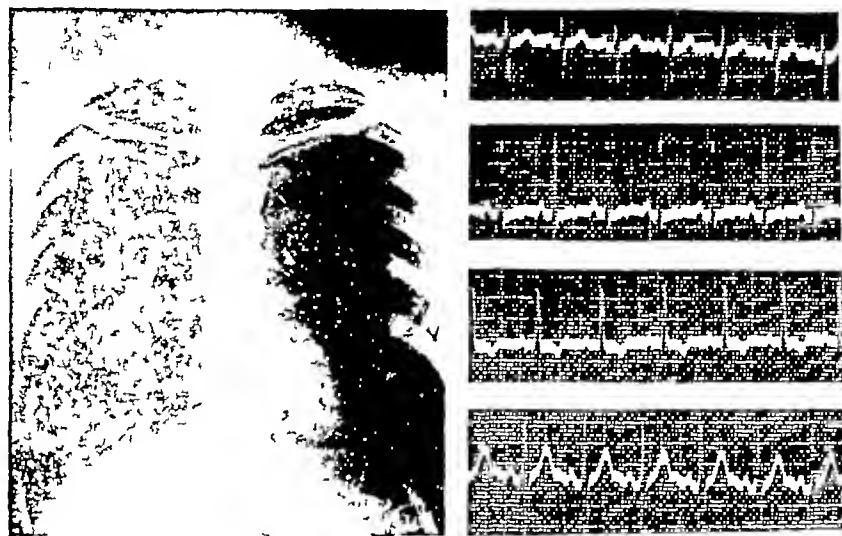


Fig 46—D McA W., seaman 2/c, aged twenty years. Enlisted in Navy August, 1942. After "chipping" paint developed sharp pain in the heart, shortness of breath on exertion, weakness and nervousness. No battle experience. Surveyed for "effort syndrome" at the U S Naval Hospital, Oakland, California, November, 1942. Blood pressure on one occasion 170/75 and pulse rate 120 per min. No organic heart disease was found. Teleoroentgenogram disclosed a depressed diaphragm and a small heart. The electrocardiogram revealed a QRS, small relative to that in Leads II and III, a tendency to right axis deviation and inversions of  $T_2$  and  $T_3$ .

hypoplastic aorta. The effort syndrome usually occurs in slender persons of asthenic habitus. The x-ray film shows a low diaphragm and a small heart, usually narrow,<sup>4</sup> (Figs 45, 46). The "small heart" is genuinely decreased in size, both in the ordinary posterior-anterior view and in the lateral view. The total transverse diameter in the posterior-anterior view is usually between 9 and 12 cm, which is definitely below the average adult size of 12 to 14 cm or more. It is easy to recognize the "small heart" on the x-ray film or during fluoroscopy if one looks for it. The heart is usually long and slender with the long axis practically vertical. The electrocardiogram, too, is typical for this small heart.<sup>4</sup>

A low QRS in Lead I and a relatively or absolutely large QRS in Leads II and III (Figs 1, 2) is characteristic of the "small heart" in the patient with neurocirculatory asthenia or effort syndrome. In fact, a right axis deviation of the QRS is not uncommon.

#### SYMPTOMS AND SIGNS

The material for this investigation included twenty-eight patients observed in the west coast Naval Hospitals at Oakland, Mare Island, Treasure Island and San Diego in a study of war casualties in December 1942 (see tabulation). The patients for the most part had broken down soon after reaching the training camps, usually within a few weeks. In a few cases the break-down followed an illness such as grippe, German measles, upper respiratory infection or appendectomy. Three men reached the combat zone before symptoms appeared but none was actually injured. Two were under fire and the third was exposed to underwater blast. All the men were unable to stand the physical and mental strain of the Navy. It is noteworthy that they gave a history of inadequacy under effort or emotion all their lives or for many years. The following cases are presented briefly to illustrate the chief symptoms.

but no evidence of myocardial weakness. The patient stated he had been subjected to palpitation, shortness of breath and weakness since 1913 when his feet were frozen.

CASE IV—M. K. S. (No. 19, tabulation), enlisted as a private, U. S. Marine Corps, January 15, 1942. He was on active duty for five months when he complained of palpitation, weakness, dizziness, nausea and vomiting. At the U. S. Naval Hospital in San Diego, he was found to be 71½ inches tall and but 140 pounds in weight. The blood pressure was 96/86 and the heart rate varied between 100 and 144 per minute. The teleoroentgenogram disclosed a small heart. The electrocardiogram showed a very small QRS in Lead I and a tall QRS in Leads II and III, with depressions of RS-T and semi-inversions of T waves in the latter leads. At the age of twelve his family physician had prevented him from participating in school athletics because of his complaints.

CASE V—R. A. W. (No. 21, tabulation), a private, U. S. Marine Corps, aged twenty-five years, enlisted October 29, 1941. He did well on light duty while at the Naval Air Station, Jacksonville, Florida, but at Camp Elliot, California, he was given heavy duty and broke down. He was tired, nervous, "jerky" and was admitted to the San Diego Naval Hospital. He was 67½ inches tall and 135 pounds in weight, i. e., he was of asthenic build. A systolic murmur was present at the apex. The heart rate varied between 80 and 120 per minute, the blood pressure was 110/85. The electrocardiogram disclosed a small QRS in Lead I. Ever since childhood he had been nervous, "blinked" and "gone to pieces when he works hard."

From these case reports and from the data presented in the table, it will be seen that the patients possessed the classical signs and symptoms of the effort syndrome or neurocirculatory asthenia. They were young adults of *slender build*. The average age was twenty-seven years, only six were over thirty years of age.

Two-thirds complained of *weakness* or *fatigue* on ordinary moderate exertion or on heavy duty—work which was well tolerated by their shipmates. A *rapid heart action* was present in fifteen of the twenty-eight patients and in addition a few had actually experienced attacks of *paroxysmal tachycardia*. Ten complained of *palpitation* or *irregular heart*. *Precordial* or *substernal pain* was present in nine, and three others suffered from "*painful*" *heart action*. The precordial pain appeared in many after physical effort. *Shortness of breath* was present in nine, one man was orthopneic, one suffered from a smothering sensation.

For the rest, "*nervousness*," a "*shaky feeling*" or a "*trembling*" were common symptoms. *Sweating* and *cold hands* were not uncommon complaints. In half the patients there was a history of *fainting*, *dizziness*, or *vertigo* in the standing position, on rising or on change of position.

Practically all the patients had a *systolic murmur* at the mitral area.



as well as a coarse *systolic thrill*, actually a "pseudo thrill." Thus, this type of case may be mistaken for one of organic mitral valve disease.<sup>4</sup>

Blood pressures indicating *hypertension* were recorded at one time or another in six patients. These were undoubtedly emotional reactions or possibly related to the tachycardia so frequently observed. These asthenic persons are probably not prehypertensives or potential hypertensives, as the rapid heart indicates. Dr. Arthur Fishberg<sup>5</sup> believes this is a means of differentiation from a true hypertensive blood pressure reading, in which case a normal or slow rate is found.

#### COMMENT

It seems to me that the expression "small heart syndrome" describes best the condition discussed in this paper. This syndrome no longer should be considered primarily a functional or nervous disorder but is actually a constitutional organic disease. A number of observations favor this point of view. As already stated, the small heart—small when viewed both in the frontal and lateral planes—is itself presumptive evidence of organic inadequacy. The patient tires on effort. He often has precordial pain, either spontaneous or on exertion. In fact, cardiac symptoms such as shortness of breath and palpitation, are apt to follow effort, a chain of events frequently observed in organic disease of the heart. Tachycardia is usually present and is probably a response to maintain an adequate circulation.

After standard exercise, such as the "two-step" test, there is a lag of the systolic blood pressure and pulse rate beyond normal limits.<sup>6</sup> The pulse lags in practically every case. This is not observed in normal persons.

*The cardiac output is diminished.* Starr and his co-workers<sup>7</sup> in 1934 found in neurocirculatory asthenia that, "although the symptoms occurred chiefly on exertion the circulations at rest were highly abnormal. The average cardiac output, stroke volume and heart work per minute and per beat were all far below normal. The arteriovenous oxygen difference was abnormally large so these patients doubtless had a lowered oxygen tension in the tissues. Except for the size of their hearts, smaller than normal, their average closely resembles those secured in patients with undoubted myocardial disease." Furthermore these authors stated that the output of the heart and indeed its work are limited by the amount of blood returned to it through the veins. If this is inadequate, no effort on the part of the heart can increase the circulation.

Haldane, Meakins and Priestly<sup>8</sup> believed that the breathlessness on exertion, rapid pulse, fainting attacks, giddiness, exhaustion, lassitude and so forth, of the "irritable heart" were such as would arise if the person was short of oxygen. They wrote, "In fact the patients are in the same state as a normal individual at high altitude where the oxygen

ished oxygen tension of the inspired air produces the same series of effects" Furthermore, these authors found that the symptoms of these patients could be relieved by the administration of oxygen and that also the amount of work they could perform was then increased Hick, Christian and Smith<sup>10</sup> reported insufficient oxygenation of the blood

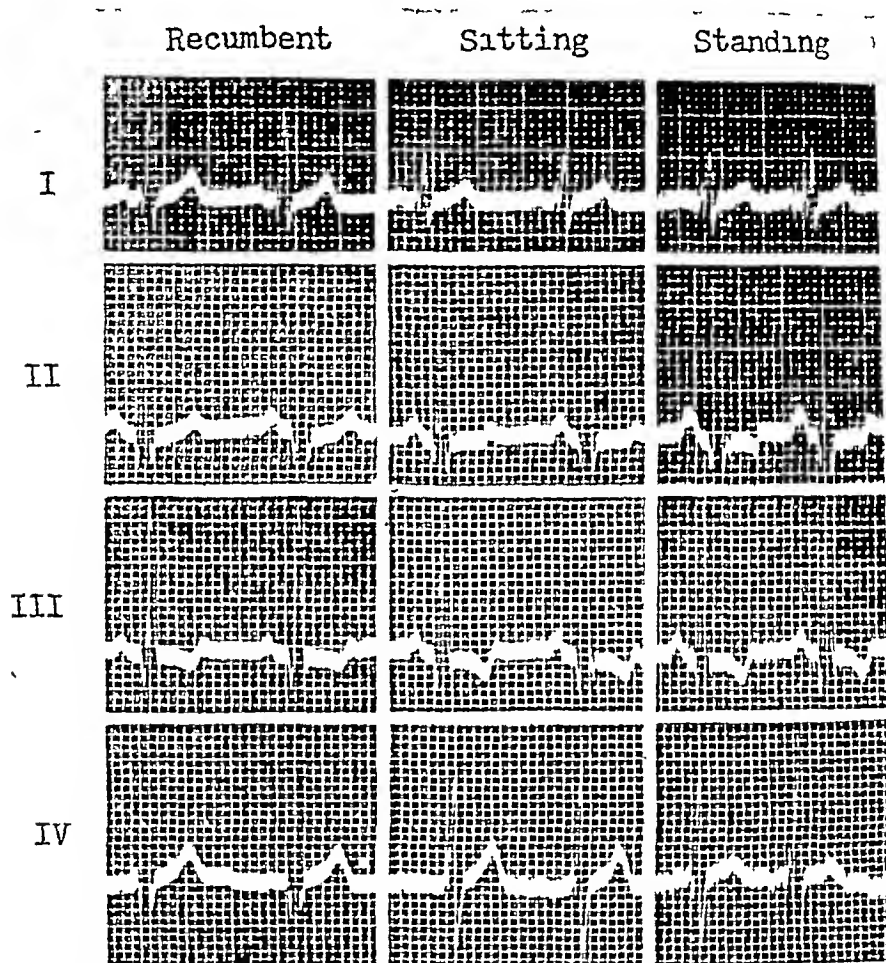


Fig 47—J S C, an apprentice seaman, aged twenty years, U S Naval Hospital, Bethesda, Maryland Small heart syndrome (effort syndrome) Control electrocardiogram in recumbent position normal In sitting position (45 degree Adirondack chair) T<sub>2</sub> semi-inverted and T<sub>3</sub> definitely inverted The same changes appear on standing and RS-T<sub>2-3</sub> are slightly depressed

in neurocirculatory asthenia similar to that seen in decompensated organic heart disease They concluded that the oxygen unsaturation of the blood produced the symptoms of fatigue, shortness of breath, and so on They also discovered that when the patients breathed pure oxygen the blood oxygen figures returned to normal

The fainting on standing so often complained of by these patients is probably due to *lack of adequate venous blood return to the heart*. MacLean and Allen<sup>11</sup> have emphasized this point. MacLean<sup>6</sup> has modified the Flack Test<sup>12</sup> and has the subject stand and blow against a column of mercury 30 mm high for ten seconds. The patient becomes pulseless and may faint, indicating a diminished venous return. The electrocardiograms of those patients taken in the recumbent, sitting and standing positions bear this out. Thus T waves may be normal and upright when the patient is in the recumbent position but frequently become diphasic or inverted in the other positions (Fig 47). The RS-T intervals may be depressed at the same time. These changes

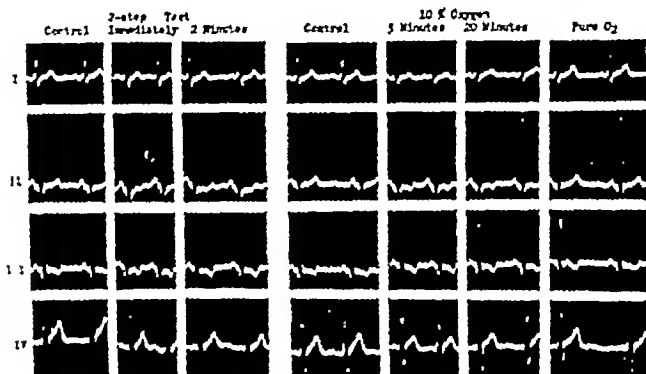


Fig 49.—J. S. C., an apprentice seaman, U. S. Naval Hospital Bethesda, Maryland. Small heart syndrome (effort syndrome). Control electrocardiogram normal. Immediately following the "2-step" exercise the RS-T segments are depressed in Leads II and III and T wave semi inverted in Lead II. This is still present two minutes later. Exactly the same electrocardiographic changes appear as early as five minutes after breathing reduced oxygen for twenty minutes.

are usually seen in Leads II and III. These changes may be taken to indicate coronary insufficiency as a result of insufficient venous blood return to the heart. Occasionally these patients have RS-T depressions and T wave inversions in the recumbent as well as in the sitting. These changes probably represent cardiac inadequacy. Some authors consider them not significant.<sup>13</sup>

Patient with a small heart show similar abnormal electrocardiogram after the standard "two-step" exercise protocol and T wave inversions and are not infrequent. (Fig 49). They are indicative of a picture resulting from coronary insufficiency,

# SUMMARY OF FINDINGS IN TWENTY-EIGHT CASES OF NEUROCIRCULATORY ASTHENIA IN WEST COAST NAVAL HOSPITALS

Case No.	Name	Hospital	Age	Ht. in Inches	Wt. (Lbs.)	Pulse	Blood Pressure	History	Enlistment to Symptoms	Heart X ray	Electrocardiogram					Angle
											R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	S <sub>4</sub>	
1	W L B	Mare Island	36	69	147	102	138/80	Flu, 1937, followed by fatigue and tachycardia. Recurrence after appendectomy in 1941. Fast heart, shaky, nervous, frightened on exertion.	4 mos.	Small	5	10		4		55°
2	C G		25				100/50	'Always' had headache, dyspnea, nervousness and tachycardia and sensitive-ness to heat.	9 mos.							
3	F A G		24	71	102	72	110/70	Nervous since age 17 when under tension. Tachycardia, nausea, vomiting, dysp-nea and trembling since being under fire.	After action		5	13	7			62°
4	J G J		17	71	100	80	170/70-0	Precordial pain, dyspnea for 1 year		Long, narrow	Tendency to right axis deviation					90°
5	K A M		21	70	165	100	145/95	Fast heart since confined to bed as child for 'leaky heart valve.' Palpitation, weak, nervous after enlistment 8/41 and after gunfire 12/7/41	1 day 6 mos	Small	6	17	10			
6	J R.		42	66	153	100	126/88	Sinus tachycardia on re-enlistment 7/16/41. Precordial pain, tired		Narrow	7	18	12			69°
7	J H S			67½	123	180	120/82	Paroxysmal tachycardia. Palpitation, dizziness, smothering, increased heart rate. History for 2-3 years. Worse seven weeks after enlistment	7 weeks Always	Narrow	1	4	8	10		110°
8	L S. S.	"	22	71	140	Up to 153	125/75	Frequent fainting since age 15. Tachy-cardia, weakness, dyspnea since en-listment	1 day	Long narrow, small	Right axis deviation					
9	R. E. S.	"	19	69½	134	112	124/90	Paroxysmal tachycardia. For 4 years painful and rapid heart action on exer-cision, on motion or change of position. Always nervous.	Always	Small	RS-T: slightly depressed					
10	E. W. B	San Diego	30	69	104	100-120		Pain in chest and nervousness all his life. Sweats.	Always	Small	6	15	11			70°
11	L. A. F	"	51	68	161		134/86	Symptoms of effort syndrome.	Few months	Small	3	25	8			84°
12	J H.	"	21	72	175	88-120	110/85	Irregular heart. Palpitation, dyspnea and precordial pain on exertion	1 month	Small, narrow	7	18	3	11		88°
13	A. L. J		48	60½	125	74	115/75	Weakness, especially on effort. Loss of weight.	Always		4	4	10	14	8	90°
14	C K	"	30	74	185	98-118	142/70	Dizziness. Rapid heart. Vertigo. Hobo once.	1 month	Small	7	16	10			66°
15	H P K.	"	46	68½	125	110	140/90	Nervousness, sleeplessness. Anorexia. Ten pounds loss of weight in 5 months.		Small	10	17	7			83°



graphic abnormalities are reduplicated in the same patient on breathing 10 per cent oxygen for twenty minutes<sup>14</sup> (Fig 48) These changes in the electrocardiogram are not due to hyperventilation, as was considered in a recent paper,<sup>15</sup> for the "two-step" exercise is equivalent to a minute and a half of ordinary walking and does not produce excessive ventilation In any case, they are observed in patients who breathe normally after the exercise or whose breathing is very little altered when undergoing the 10 per cent oxygen test.

That the symptoms of effort syndrome or neurocirculatory asthenia are largely the result of the long, narrow heart is indicated by the fact that *the incidence of a small heart is very much higher in this syndrome than in other types of functional heart disease or in the general population* Thus, in a series of forty-two patients in whom a diagnosis of neurocirculatory asthenia was made at the National Naval Medical Center, Bethesda, Maryland, 1942-43, all but three showed a small heart by teleoroentgenogram and fluoroscopy This is an unusually large incidence of "small heart" On the other hand, only 21 per cent of a control series of 100 functional cases were found to have a small heart These cases were seen in consultation at the same time as the above cases and consisted of fifty-eight with systolic murmurs, six with precordial pain, six with tachycardia, and a miscellaneous group of thirty with possible hypertension, rheumatic heart disease or Graves' disease Even the incidence of 21 per cent in this group is liberal since there probably were instances of neurocirculatory asthenia with small hearts in the fifty-eight patients referred because of questionable murmurs Thus, a small heart was found in practically all the cases of neurocirculatory asthenia, but in only a small percentage of functional cases without the typical symptoms of effort syndrome

It has not been the intention in this paper to cover the entire literature on the subject of effort syndrome or neurocirculatory asthenia This has been done well by contributors to this topic<sup>16, 17 18 19 20 21</sup> Instead, the conception that the small heart is of a constitutional nature and produces the "small heart syndrome" has been emphasized

### CONCLUSIONS

The "small heart syndrome" is seen in asthenic persons with constitutionally small hearts who present the symptoms ordinarily called effort syndrome or neurocirculatory asthenia

The small heart syndrome (effort syndrome or neurocirculatory asthenia) is a definite problem in the Navy as it is in civilian life Persons with it break down shortly after enlistment under the physical and mental strain of the war and they should not be accepted for general service in the Army or Navy They are, however, often adequate for limited service just as they may be in civilian life

The most frequent complaints are fatigue or weakness on effort, rapid heart, precordial or chest pain, also frequently on effort, shortness of breath, nervousness, trembling, sweating and fainting.

The small heart syndrome (effort syndrome or neurocirculatory asthenia) is the result of a congenital or constitutionally small heart. It should no longer be considered merely a nervous or functional disorder. Evidence of the organic nature of the condition are the cardiac complaints including precordial pain, shortness of breath, tachycardia, lag in return of the blood pressure and pulse rate to standard exercise, abnormal electrocardiogram in the sitting position, diminished venous return on sitting, standing or on exercise, a proclivity to fainting on standing an abnormal electrocardiogram after standard exercise, indicating anoxemia of the heart muscle diminished cardiac output and finally decreased oxygen saturation of the blood.

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## SOME GENERAL OBSERVATIONS ON CARDIOSPASM

ASHER WINKELSTEIN, M.D.\*

SOME years ago I reviewed the etiology of cardiospasm and stressed the idea that cardiospasm was the result of a dysregulation of the cardia and that, while it may be produced in various ways, one of the chief causes seemed to be psychic.<sup>1</sup> Eight cases were cited in which emotional disturbances apparently initiated and carried on the disease. Psychotherapy was found to be of value, even curative, in early cases. In advanced cases, psychotherapy may relieve the symptoms but the esophageal dilatation persists. Since publishing this paper, a fair number of cases has been observed. It is the purpose of this communication to comment on some interesting features of these cases.

### ETIOLOGY

Certain ideas concerning the cause of this disease should be discarded. The evidence for the following theories is slight indeed: (1) Congenital mega-esophagus, or, a primary atony, (2) "liver tunnel" diaphragmatic constriction, or angulation, (3) spasm at or near the cardia, and (4) ovarian or other ductless gland disturbance. After years of observation and study, one is forced to the conclusion that the majority of the cases are examples of a psychosomatic disturbance. An exquisite example was seen recently.

CASE 1—A girl aged nineteen years, at the age of fourteen was taken into the woods and raped by a man of fifty. He threatened to kill her if she informed her family. The next day dysphagia and regurgitation set in and persisted for five years. Radiography revealed a widely dilated esophagus with food retention for several hours. After the first sexual incident this girl had numerous sexual affairs with various men voluntarily. She lived in constant dread of discovery by her parents who considered her a model child.

Since numerous cases have been encountered in the last ten years which illustrate the point it does not seem necessary to add further examples in proof of the psychosomatic theory.

A few cases seem to substantiate the idea that organic disease involving the vagus nerve can cause the condition. Two cases may be described briefly in illustration.

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\*From the Cardiology and Clinic of the Medical Division, The Mount Sinai Hospital, New York City.

Associate in Medicine and Chief Gastrointestinal Clinic Mount Sinai Hospital, Associate in Medicine Post-Graduate Medical School, Columbia University.

CASE II—A woman of fifty-two exhibited all the symptoms and radiographic signs of cardiospasm. Despite a negative esophagoscopy, it was decided because of her age and a short history, to explore the abdomen. The cardia was found wide open but a biopsy of the somewhat thickened mucosa revealed a diffuse infiltration with lymphosarcoma.

This case seems to support Hurst's views that cardiospasm (or, achalasia of the cardia, as Hurst prefers to call it) is due to organic disease of the Auerbach's plexuses at the cardia.

CASE III—A woman of thirty-seven had a healed, bilateral, upper lobe tuberculosis. The upper mediastinum was pulled over to the left. In view of the fact that the symptoms of cardiospasm appeared as she was recovering and that numerous calcified areas were seen in the mediastinum, it is logical to conclude that the cardiospasm in this case was due to the involvement of the vagus nerve in the tubercular scar tissue.

Experimentally, in the dog, cardiospasm may be produced by sectioning the vagi in the middle of the chest. Friedrich Krauss has described a case like Case III and Assman one like Case II. Apparently, organic as well as functional involvement of the vagus nerves may cause cardiospasm.

A few cases seem to be reflex. One such case has been under observation for fourteen years.

CASE IV—A man of twenty-six years had symptoms which had commenced at twelve. Repeated radiographs and esophago-gastroscopy revealed a small gastric diverticulum in the lesser curvature of the stomach just below the cardia.

#### PATHOLOGY

There is no evidence of spasm of the cardia. It has not been seen with the esophagoscope. At operation, or postmortem examination, there is no thickening of the musculature at the cardia.

As a rule, there is a rather marked, secondary, esophagitis. This may add to the vicious circle by involving Auerbach's plexuses.

Once the dilatation is of long standing, the esophagus does not return to normal. The emptying rate may increase and the patient improves clinically, but the dilatation remains.

A small percentage of the cases develop not only a wide esophagus but a long and redundant one. The figure-S type is occasionally encountered. This poses considerable difficulty both in study and treatment.

Pulsion diverticula in the lower esophagus are not rare.

True, solitary peptic ulcer of the lower esophagus is not seen as a complication of cardiospasm.

## DIFFERENTIAL DIAGNOSIS

Despite xouth and typical radiographs, esophagoscopy is imperative in order to exclude carcinoma and lymphosarcoma. We have seen a case of a woman of twenty six treated for six months for typical cardiospasm who, with esophagoscopy, was found to have an adenocarcinoma of the cardiac end of the stomach<sup>1</sup>

*Peptic esophagitis*, a new clinical entity described by the author several years ago<sup>2</sup> must be differentiated from cardiospasm. The diagnosis is not too difficult. Peptic esophagitis is an erosive, hypertrophic, inflammatory lesion of the lower third of the esophagus, often associated with gastric or duodenal ulcer occurring chiefly in elderly males. The radiographs are characteristic. They suggest, because of an irregular narrowing, neoplasm rather than cardiospasm. There is little or no dilatation over the stenotic area. The symptoms usually respond to anti ulcer therapy, particularly the milk-soda drip as devised by the author for the treatment of gastro duodenal ulcer.<sup>3</sup>

## THERAPY

Psychotherapy is of great value in all cases. It may prove curative in very early cases. Improvement should be judged by the subjective state and the increased rate of emptying of the esophagus. The dilatation as stated, rarely recedes.

In the advanced cases with marked dilatation but with a straight esophagus *mechanical dilatation* is imperative. We are averse to the Plummer-Vinson hydrostatic dilator since it may cause esophageal rupture in a small percentage of cases. This is true also of all the straight stiff bougies with graduated olive tips. For several years we have used successfully the soft, mercury-weighted, rubber esophageal bougie of Hurst. This is based on the observation often seen under the fluoroscope that weight alone will open the cardia. The bougie contains 1 pound 5 ounces of metallic mercury and is usually 40 F in diameter. At first it should be passed before meals by the physician. Then the patient learns to introduce it. After a few weeks it may be passed once a day then every other day and then a remission is in order. When the symptoms recur, it may be used frequently again. This form of treatment is often successful. It is inexpensive and harmless. True it does not effect a lasting cure. Occasionally a wider tube (50 or even 60 F) works better. Whether the effect is mechanical or psychologic (phallic symbolism?) cannot be answered in the light of our present knowledge.

Since atropine is equivalent to vagotomy its use is contraindicated.

Methods to increase esophageal peristalsis (carminatives, hot drinks, charged water) are more logical. General nerve sedatives and bland soft diet were desirable.

*Local diathermy*, using the Brunner-Ornstein method, tried only in a few cases, was not successful in our hands

With Dr William Bierman, I treated some cases with *artificial hyperpyrexia* <sup>4</sup> Six to eight treatments, every other day for two to three hours, to a temperature of 102–103° F were given in four cases Subjective improvement and increased motility of the esophagus were noted This harmless method of therapy deserves further study Dr Henry Doubilet, using a balloon in the cardia, was able to demonstrate effective relaxation during the artificial hyperpyrexia

In the patients with an elongated and redundant esophagus, the *Heyrovsky operation* is useful and usually successful The esophageal hiatus is widened, and the lower, dilated loop of esophagus is pulled down and anastomosed to the upper anterior stomach wall In one of my cases in which the greatly elongated figure-of-S esophagus did not completely empty itself of a barium meal in two weeks, after the Heyrovsky type of operation it emptied in one hour In three months, the patient gained 30 pounds

#### SUMMARY

Cardiospasm is, in most cases, a psychosomatic disease Organic disease of the vagus nerve and reflex causes are also of etiologic significance It is not a spasm but an achalasia (failure actively to open) The dilatation persists despite clinical improvement Elongation, esophagitis and diverticula may develop

Esophagoscopy is imperative to exclude neoplasm and peptic esophagitis Psychotherapy and the soft mercury-weighted rubber esophageal bougie are the two best forms of therapy for the patients with a straight, dilated esophagus For patients with an elongated, figure-of-S esophagus, esophagogastrostomy is indicated Artificial hyperpyrexia deserves further study as a therapeutic agent

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## NONSPECIFIC ULCERATIVE COLITIS AS A PSYCHOSOMATIC DISEASE

GEORGE E. DANIELS, M.D.\*

### DEFINITION CLINICAL AND PATHOLOGICAL PICTURE

Nonspecific ulcerative colitis is an inflammation of the large bowel including the rectum without known etiology, occurring in cycles and usually accompanied by diarrhea with sanguineous and/or mucopurulent discharge. The lower portion of the bowel is most frequently involved, but the process may be generalized. The amount of discharge depends on the severity and degree of involvement. Diagnosis is made by sigmoidoscopy. The absence of haustrations as seen by x-ray is significant. Characteristic miliary ulcers are seen which break down and form abscesses. There is often muscular hypertrophy, the rectal muscles and the tenia being most commonly affected.<sup>12</sup> The lumen of the bowel may become enlarged or narrowed. In the latter instance spasm may be responsible or cicatrization may have led to organization and permanent blocking necessitating operation.

In two sisters, suffering from ulcerative colitis and treated at the Presbyterian Hospital in New York City, x-ray showed tortuous pipe-like sections of bowel, described in one case as a "narrow linear streak of barium." Operation was seriously considered. The stricture in both cases disappeared after a month or two of intensive psychotherapy with resultant decrease of emotional tension. The ulceration may be so extensive and confluent that a large part of the mucosa may be removed. Polypoid outgrowths between the ulcers frequently make their appearance. Ulcerative colitis from neoplasms, diverticulitis and persisting after the disappearance of the organism in bacillary or amebic dysentery should not be included in this group.<sup>13</sup>

The condition occurs in children. A group of nine cases has been studied by Dr. William Laneford at the Baby's Hospital at Columbia Medical Center. Four of these were followed for psychotherapy for periods varying from six years to seven months. Treatment of the family situation proved an important factor in improvement.<sup>14</sup>

### CONTRIBUTING FACTORS

As the various terms nonspecific idiopathic primary suppurative and indeterminate ulcerative colitis imply, the etiological agent is unknown. One agent has been described, but their etiological

\*Clinical Professor of Psychiatry, College of Physicians and Surgeons,  
Columbia University.  
1160 J. L. 1133

not been established. Barger attributed the condition to a gram-positive diplococcus and developed a serum for its control.<sup>3</sup> The results, on the whole, have been disappointing. Avitaminosis is thought to be a contributing factor and ulceration of the colon in lower animals has been produced by vitamin deficiencies.<sup>12</sup> Constitution and heredity are undoubtedly important.

Cecil Murray was the first to study systematically *emotional factors* in ulcerative colitis as a result of routine personality reviews in the Constitution Clinic of the Presbyterian Hospital, New York City, under Dr. George Draper. A report on twelve cases was made by Murray in 1930.<sup>6</sup> Albert J. Sullivan, stimulated by one of Murray's cases seen at the New Haven Hospital, studied, treated and reported fifteen cases in 1936.<sup>14</sup> Sullivan estimates that 75 per cent of cases have the psychogenic factors as primary.<sup>12</sup> Wittkower published an article in 1938 on personalities found in forty ulcerative colitis cases studied at the Travistock Clinic at St. Bartholomew's Hospital in London.<sup>16</sup> and Daniels reported a group of fourteen cases in 1939.<sup>6</sup> Subsequent investigation bears out the early findings and increasing reference to psychological factors in the disease is appearing in the medical literature.

### COURSE AND OUTLOOK

Ulcerative colitis occurs in a fulminating form that runs a few weeks' course and is often entirely resistant to treatment, and in a chronic form with remissions during which the patient may be comfortable and fairly active. The mortality figures range from 33.5 per cent by Hardy and Bulmer<sup>9</sup> in all cases over a period of twelve years, to 10 per cent by Barger and Buie<sup>8</sup> in a ten-year period at the Mayo Clinic. Spriggs<sup>13</sup> reports 20 per cent in nineteen years, Buzzard, Richardson, and Turner<sup>4</sup> and Hern<sup>10</sup> give the figure as 28 per cent. Of those patients who survive and are not surgically treated, about 75 per cent are considered well enough during remissions to earn a living. Attacks often last for many months, often necessitating hospitalization. The outlook for patients who are suitable for psychotherapy is definitely better if this can be employed. Improvement obtained in these cases cannot be explained by spontaneous remissions or general medical procedures alone. Individual attacks may be cut down considerably in time, attacks that might last into weeks and months made abortive, and remissions sustained for years. It is questionable, however, whether, once established, the condition is ever "cured."

### PERSONALITY STRUCTURE AND DEVIATION

The personalities discussed in this section represent the findings in the relatively small number of cases studied and reported and should not be considered a generalization for all cases.

The ulcerative colitis personality is apt to be *self-centered* (narcissistic) and *dependent*. The dependency is shown particularly toward the mother or a mother substitute, frequently an older sister. This dependency is often maintained by the involved parent or substitute at the expense of the patient, especially through fostering illness under the guise of care. One patient's remark that "my mother would rather have me sick at home than well and away" represents a frequent, if often unconscious attitude on the mother's part. This same patient stated that in line with the saying "My Country right or wrong" her version was "My Mother right or wrong." Dominating in-laws frequently take over this family role.

As would be expected in dependent persons, many ulcerative colitis patients are *emotionally and sexually immature* and do not carry responsibility well. They are apt to break in a crisis and the Yale Group has dubbed them the "giver-uppers." In this they are the opposite of the peptic ulcer patients who are aggressive as a rule and seek responsibility. The males are inclined to be of the passive type pathologically attached to their mothers and frequently unmarried. Of Murray's original series of fifteen cases, seven were men and none married. The women who are more frequently married are apt to be of the "fussy" type of housewife with a marked sense of neatness.

Wittkower<sup>18</sup> found that *psychiatric disorders* were far more frequent than in the average population. These manifestations antedated the colitis and were so gross that a special control group was not deemed necessary. He found no uniform personality make-up but his cases fell into three groups, with common characteristics within the group, a fourth group consisted of the miscellaneous personality types. The first group was characterized by obsessional traits, the second which was made up entirely of women by hysterical traits and the third by depressive or schizoid trends. The personalities in childhood coincided with those in adult life except that there was often an exaggeration of characteristics after maturity.

*Mental depression* in association with the disease is a frequent finding and important in the psychotherapeutic approach. When it is consciously present, the physician may be misled into thinking that it is a legitimate secondary reaction to an uncomfortable and disgraceable disease thus neglecting a valuable indicator of primary emotional disturbance. In other cases there is no conscious awareness on the part of the patient that he is depressed the whole affective reaction being masked by the physical symptoms only to make its appearance in its original form during psychotherapy. Care must be taken in severe cases not to precipitate the depression too rapidly. In some instances a strong unconscious suicidal drive appears to be an important factor in the severity of the disease process. The depression is usually reactive in nature, that is following some loss or frustration. The cyclic character

acter of ulcerative colitis and manic-depressive insanity suggests a possible relationship and one that deserves further study

Psychosomatic manifestations other than diarrhea frequently appear in the same case. Various *hysterical conversion* and *anxiety* symptoms are common. In two cases studied, attacks of ulcerative colitis, asthma and tachycardia displaced one another, in one of the cases occurring successively as psychotherapy progressed. Many patients notice a decline of their mental symptoms with the increase of their bodily ones.

#### PRECIPITATING FACTORS

The striking, often dramatic, relationship between the onset or recurrence of an ulcerative colitis and *emotional disturbance or conflict* makes it frequently possible to identify the situation or event without deep or prolonged investigation. Frequently, as pointed out by Sullivan,<sup>14</sup> the symptoms break out within forty-eight hours of such experiences. Dr. Chester M. Jones, in discussing Sullivan's cases, reported on 100 cases seen with Dr. Urmey at the Massachusetts General Hospital.<sup>14</sup> In two thirds of these cases they considered psychogenic disturbances to be obviously responsible for bringing on exacerbations, and in the whole group they felt that acute upper respiratory infections, emotional upheavals and possibly pregnancy were the most obvious elements entering into the onset of the disease.

The influence of *pregnancy* appears to be more from the emotional strain and conflict than from physical factors. As has been pointed out, the rigid and immature personalities of the majority of these individuals makes them unable to tolerate reverses or crises well or to undertake the normal steps in emotional and sexual maturity of engagement, marriage and childbearing. Many women get safely through pregnancy but an attack is precipitated after childbirth. In the men, a frequent conflict is that between attachment to the mother and a desire to get married. Sickness or death of a near relative, particularly the mother, is especially traumatic. Losses of money or financial worries play a prominent part in many cases.

Murray has emphasized the fact that it is not a sudden fright which causes the difficulty, but a new situation which thereafter acts to keep the patient in a constant state of apprehension. Such a state was that of a forty-eight-year-old housewife who had suffered intermittent diarrhea for eleven years which she developed when she left the hospital with her first child.<sup>6</sup> Information obtained showed that she had been unable to become pregnant for fourteen years and when she did she attributed it to another man. This led to a great deal of conflict as the child was accepted without question by her husband. She had never told anyone about the circumstances, not even her sister, and remarked that *not a single day passed in all this time without its being on her mind*. These patients have a very ambivalent attitude (mixture



of love and hatred) toward those to whom they are attached, and symptoms frequently are an expression of repressed resentment and hatred

#### UNDERLYING PSYCHOPATHOLOGY

Diarrhea is a common expression of anxiety and fear. At a deeper psychological level it represents a regression to an early state in infancy and childhood. As such it may be an expression of a desire or demand to be cared for and tended, which in the practical nursing of these patients, in the acute stages, becomes a constant necessity. In order to understand what, psychologically, lies back of many of the symptoms in psychogenically motivated diarrhea it must be remembered that the infant has quite a different attitude toward the excreta than the adult. He enjoys soiling and may even think of the excreta as something valuable or later thinks of it as something poisonous or destructive. Symbolically, money and feces are often equated. This was strikingly evident in one of our patients who while having active diarrhea, enjoyed fantasies of coming into a lot of money and of presents she would give herself and family. Alexander has pointed out in his spastic colitis cases<sup>1, 2</sup> that the diarrhea often represents a compensation for inadequacies which the patient tries to make up for by the giving of feces, and that the obligation of being cared for and supported is often compensated in this infantile symbolic manner. Alexander also emphasizes a fact long known to psychoanalysts that the feces may be considered an instrument of aggression.

The equation in the infantile mind between feces and baby is another attitude that persists in the unconsciousness of adults and plays a role in psychogenic diarrhea including some cases of ulcerative colitis with immature sexual attitudes. One patient reported<sup>3</sup> went through the remarkable experience of giving birth to an eight-month fetus into the toilet without experiencing any pain or conscious awareness of what was taking place.

#### PSYCHOPHYSICAL MECHANISMS

In the cases in which the psychogenic factors seem to predominate the mechanism by which the lesion are brought about is not clear. The autonomic nervous system particularly the parasympathetic appears to be particularly important. It is known that the descending colon and probably the entire colon receives parasympathetic stimulation. White, Cobb and Jones in reviewing the literature, cite the findings of Watts and Lukon that following production of artificial hypothalamic lesions in monkeys, extensive lesions were found throughout the gastrointestinal tract. They also confirmed the findings of Cushing of the influence of gastric and duodenal ulcerations seen in patients operated upon for brain tumors in the hypothalamic region and quote the works of

Banting and Hall These investigators administered acetylcholine intravenously to dogs over periods of days and demonstrated extensive hemorrhagic ulcerations of the stomach, small and large intestines.

Sullivan suggests that the stimulation of centers in the diencephalon due to emotional stress and the consequent whipping up of peristalsis in the small intestine may lead to the emptying of abrasive digestive juices into the large bowel or that the enzymes may be more potent in these cases or the mucosa less resistant In any event, surface digestion of the mucosa occurs which makes bacterial invasion easier, and ulceration results Because of the patient's inability to solve his problem, hypermotility of the intestine persists with constant irritation and chronic colitis The work by Wolf and Wolff demonstrating hyperemia, hypermotility and hyperacidity of the stomach mucosa, due to emotions, and their ability to produce small ulcerations on the mucosa of a patient with a permanent gastric fistula by removal of the mucous protective coating shows a comparable mechanism in the upper intestinal tract.<sup>17</sup>

#### THERAPY, INCLUDING PSYCHOTHERAPY

The general medical and surgical treatment of ulcerative colitis will not be gone into in detail here General medical care and supportive treatment is essential Reference can be made to standard textbooks on this subject In general, both of these approaches are disappointing insofar as specific therapeutic measures go, treatment being chiefly symptomatic A multitude of procedures are employed, including vaccines, serums and various medications such as bismuth, kaolin and belladonna Transfusions are often necessary Chemotherapy seems to give results in some cases Vitamins are usually indicated Surgery is a last resort, as to accomplish anything it has to be radical and it usually leaves the patient with a permanent colostomy

Psychotherapy in selected cases is definitely the treatment of choice As the patients are usually severely physically ill, frequent contacts with the physician over long periods of time are necessary for general medical supervision and give ample opportunity for observation, collecting of necessary history, and prolonged either superficial or deeper psychotherapy The intensiveness and the extensiveness of the psychotherapy depends on the basic maturity of the patient, severity of the neurosis, and the training of the psychotherapist

Various points on treatment have been touched upon in the preceding sections No attempt can be made in this article to outline systematic psychotherapy Reference should be made by the general physician interested in this problem to a recent book by Maurice Levine\* in which various approaches are indicated, based on aptitude and ex-

\* Levine, M Psychotherapy in Medical Practice New York, Macmillan Co., 1942

perience. Some of the cases encountered are largely situational, others have a deep neurotic superstructure which none but a psychiatrist experienced in psychosomatic medicine should attempt to treat. The problem of a domineering mother or her substitute as mentioned is one of the most frequent relationships to overcome, and the release of the repressed hostility in such cases, as well as gradual help in bringing the patient to greater emotional maturity is, in general, the chief aim of treatment in many cases.

In patients with ulcerative colitis, it is important to take a *psychosomatic history* which should include personal history, social history (including work and work relationships), sexual history, and the history of any neurotic or other psychosomatic illnesses in addition to the regular medical and surgical history. In determining significant precipitating events it is essential to remember that a direct question such as whether the patient had been worried or troubled may fail to reveal anything, either because the patient is unaware of it or embarrassed at revealing it. Obtaining a parallel history in the personal sphere, however, and comparing this with the medical data often shows striking coincidences.

It may take weeks or months of observation before relationship between the precipitating element and the diseases become clear. In the patient developing diarrhea after the birth of the child conceived out of wedlock, the significant facts were not obtained until six months after discharge when the patient was being seen for follow-up in the Out Patient Department. The relationship came out clearly in the first interview, however, in the case of a thirty-year-old unmarried mulatto woman who had attacks of ulcerative colitis of sufficient severity to necessitate hospitalization whenever she attempted to move from the home which she and a divorced sister and the sister's child shared. The sister was unsympathetic and placed upon the patient entirely unwarranted responsibilities. She was seen over a period of eight years and the therapy on the whole was quite superficial. The essential feature was for her to understand and learn to express some of the antagonism toward the sister whom she was emotionally dependent on and whom she feared. After seven years she finally did break away and met her sister's verbal onslaught with an outpouring of her own against her and was able to move to another city and reestablish herself in a way she had been hoping and planning for years. This patient was seen only an aggregate of fifteen times during the complete period and could have been handled by a general medical man with interest in "psychosomatic" aspect.

In the case of another patient with severe colitis in whom the sister figured as a point of attachment in conflict, a period of intensive psychotherapy was necessary and three months of therapy resulted in free association on the couch because of the deep

neurosis and the degree of repression. Such a case obviously could not be handled without special training.<sup>7</sup>

These patients are often hospitalized during the more acute stage of their illness and with suitable training of the staff, psychotherapy can be carried on while the patient is receiving other therapy. The privacy of a room for interviews is essential.

Sullivan reported such an approach to patients at the New Haven Hospital, outlining the general procedure.<sup>14</sup> The general medical staff handled the bulk of the psychotherapy, calling in the psychiatrist for consultation in difficult problems, or to take over the more severe neuroses encountered. Jones reported good results at the Massachusetts General Hospital, but particularly on the private wards.<sup>14</sup> The initial part of our psychotherapy in these cases at the Presbyterian Hospital is carried out by the psychiatrist while the patient is still on the ward, the psychiatrist seeing the case as frequently as may seem indicated.

It is important for the house staff and nursing personnel to understand something about the behavior of a patient under psychotherapy. First it is imperative that such a patient be treated as any other patient on the ward and not avoided because he is a subject for psychotherapy. It is also essential for it to be recognized that the patient may be upset following interviews and that this is often a necessary part of furthering recovery and not a sign that the patient is being made worse. In treatment of associated depression, for example, periods of weeping are frequently a corollary to release of tensions and recovery. If the emotional disturbance is sufficiently severe, the patient should be allowed to retire during such outcroppings, or to have the bed temporarily screened. Naturally such procedure should have direct psychiatric supervision.

It is important to recognize that emotion regarding the contributing situation or conflict is often concealed in the complaint about the physical discomfort. One such patient, in complaining about symptoms in her chest, was clearly referring to her whole conflict regarding her newborn child and the home situation.<sup>7</sup> In other cases the patient may show evident depression or agitation with the reason conscious or fairly close to consciousness. Such was the case of a thirty-year-old Italian woman who has an interfering mother-in-law who had been seeking to exercise authority throughout her marriage and to whose onslaught the patient was succumbing with marked underlying hostility and consciously experienced depression.<sup>6</sup> This patient, a chronic case, responded well to psychotherapy.

It is essential early in a case to evaluate the social factors and the degree which they can be manipulated as a part of the treatment program. If the case is being treated in a hospital the Social Service Department can be extremely helpful in collaborating with the psycho-

therapist. In one case plans for getting the patient and her family away from the parental home were laid a year in advance, long before the patient herself realized the difficulty or her ability to cope with it.

# SUMMARY AND CONCLUSION

Ulcerative colitis is a recurrent, wasting and often fatal disease with no established etiology. Investigation has shown that personality factors are important in the precipitation and recurrence of the disease. The precipitating factor is often related in time to the first forty-eight hours. Although general statements cannot be made that emotional factors are important in all cases, continued study shows that it is so for the majority. Frequently gross psychiatric disorders antedate the outbreak of the disease. Emotionally, these patients are immature and show infantile sexual characteristics. They frequently break at crises which represent a forward step in emotional sexual maturity, such as engagement, marriage and childbearing. Financial difficulty and loss of a close relative are frequently important. A fixation on the mother is an outstanding feature. Behind this lies much repressed hostility, often concealed in the symptoms.

A carefully taken psychosomatic history should be included in all cases of ulcerative colitis, with selection of suitable cases for psychotherapy. Such therapy has been eminently successful in many instances. Its application depends on the severity of the neurosis and the experience and equipment of the therapist.

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## EMOTIONAL FACTORS IN SOME YOUNG CHILDREN'S COLDS

J LOUISE DESPERT, M D \*

THE most frequent cause of absence in nursery school is the common cold. The fact that children develop colds so readily during pre-school years is often given by parents as a reason for postponing the initiation of their child to group life. Pediatricians are not agreed regarding the advisability or need of developing early immunization to causative agents. If the genesis of upper respiratory infections is stimulated by first contacts with other children, one should expect greater frequency during the first than the following years at school, but this is not always the case.

Physiological adjustments during the first year at school are further complicated by an extremely important psychological factor. It is usually the first time that the child leaves the family circle, he has to make adjustments to strange children, and to adults other than those with whom he is familiar. If he is an only child, it is also the first time that he must share the mother figure with other children. As a result, internal tensions are increased, and the repercussion of such increase on the child's resistance to infections must also be taken into account. There are considerable variations among the individual children as regards frequency and severity of colds.

Another interesting aspect of this question is the difficulty of differentiating between toxic and allergic or "psychogenic" colds, a provocative problem from the point of view of group prophylaxis, since the periods of exclusion from school should be adapted to these different forms. Rules vary from one school to another regarding signs and symptoms which determine the length of compulsory absence in the case of colds. Furthermore the attitudes of the parents, especially the mothers toward the child's illness also offer considerable variations. One mother keeps her child at home at the first appearance of minimal signs or in anticipation of such signs, whereas another sends hers to school with marked evidence of infection. Finally the children's own reactions to the enforced stay at home or in bed which entails separation from play companions diverge widely.

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In view of these multiple considerations it was thought of interest to analyze the records of the children admitted at Payne Whitney Nursery School from 1937 to 1942, five complete years, in an effort to ascertain which children develop colds more frequently, and what relations, if any, can be established between emotional adjustment and resistance to colds, and to determine what emotional factors may be involved in the frequency of colds in young children. This publication concerns itself principally with one small, well defined group of children, namely, eight children from broken homes.

#### METHOD AND GENERAL CONSIDERATION OF PROCEDURE

Personality studies have been carried out at the Payne Whitney Nursery School since 1937. Sixty-three children of ages from two to five years were studied from 1937 to 1942, according to a method for the study of personality reactions in preschool age children by means of analysis of their play, described in a previous publication<sup>1</sup>.

Besides having yearly physical examinations, the children are followed by their own pediatricians and checks are made daily by the school nurse. The policies of the Nursery School as regards exclusion from school for physical reasons are as outlined in the report of the school nurse.

In conducting the morning inspection of the children in the Nursery School it is assumed as a basic principle that the children's health is the mutual responsibility of the school and of the parents. Each child is under the supervision of his own pediatrician, and any questions which involve treatment or care of the child are referred to him. A pediatrician connected with the pediatric department of the hospital is available for advice on minor matters or in cases of emergencies and when quarantine of the school may be indicated.

When the child comes in the morning he brings with him a form which has been filled out by the mother. This form gives an account in outline of the child's eating, sleeping, elimination and physical activities and mood from the time he left school the previous day until he arrives at school the next morning. This form also records unusual signs such as overfatigue, undue irritability, loss of sleep or any unusual disturbances such as vomiting, sleeplessness and loss of appetite.

In doing the morning inspection of the children, the school nurse notes unusual signs such as coryza, inflamed throat, sneezing, coughing, skin lesions and unusual pallor or flushed appearance of the face. She also notes any deviation in the general behavior or mood of the child as he comes into the office. If any of the above signs are noted the parent is advised to take the child home. The parents are urged to be aware of these signs and to keep the child at home whenever there is any doubt of his fitness to be in school. It is emphasized that perfect attendance is not the aim for the child, and that group experience is valuable only if the child is in good physical condition. The educational influence upon the parents of observing the morning inspection and discussing aspects of the child's health with the nurse is noted as the year progresses. The nurse visits



the school informally at frequent periods during the day, thereby adding to the confidence of the child in the nurse and child relationship.

As pointed out above, parents vary considerably in their attitude toward their children's physical illnesses. In computing the absences due to colds an effort was made to evaluate absences attributable to the child's illness, and those directly referable to the mother's anxiety. Quantitatively, however, it is often impossible to separate the two, since this would require a daily check at home and a medical report of minute development. If the infection is mild, the child may not be seen by the pediatrician even though his condition warrants his stay at home, or even in bed, and the mother or the nurse is in this case the sole judge and observer. Nevertheless an attempt was made to evaluate this factor by comparing two figures: (1) the total number of days of absence for colds, (2) the number of colds for the corresponding year.

Since absences are entered in the children's school records under specific diagnostic headings, it was a simple matter to establish the order of frequency of colds for all children during the five years. Another computation was made to show the total absences for colds plus fatigue and digestive upsets, since the latter are frequently related to the former. With some of the children the absence figure, computed independently for colds, was raised considerably when absences for fatigue and digestive upsets were added, but in the majority of cases the figure remained practically unchanged. The percentage of days of absence due to colds was estimated on the number of possible days at school for each child. For purposes of comparison, the percentage of cold absences was computed separately for (a) the eight children from broken homes, (b) the remaining fifty-five children, (c) eight children selected for their good adjustment and their particularly happy homes. Age levels were taken into consideration but also the fact that the child was attending school for the first time whether in the first or second age group was considered. A special notation was also made of the teacher in charge of each group.

In an effort further to differentiate the types of respiratory infections suffered by the children, the pediatricians were asked to answer the following question: "Were these children's colds of the so-called noncontagious allergic rhinitis type or were they associated with toxic and infectious symptoms?" All children except one were thus reported as having suffered the infectious type, but most pediatricians were unwilling to establish a frank declaration between the two types. The following observations are quoted from typical reports: "I sympathize with your effort to separate colds into contagious and allergic. From my experience it is impossible to make a decision in most cases. There are occasional children who have a real allergic rhinitis and

whose noses run clear mucus most of the year without ever being really free. On the other hand, most children with frequent and prolonged colds do have periods of freedom from symptoms even if only for a few days, and when you try to ignore colds and send the child outdoors he is apt to get worse, develop more cough or some fever or an ear inflammation. My feeling about these susceptible children is that though there may well be a hypersensitiveness of the nose and though emotional tension may play a great part, nevertheless the bacteria are there, too, and cannot be ignored."

The second quotation from another report substantiates the first. "I do not know how one can be sure that a cold is of the allergic type. I know that many colds are made possible because of allergy and are harder to clear up because the mucous membrane is boggy as the result of allergy. Just because the child has a running nose and no temperature or toxemia does not necessarily mean that it is an allergic manifestation. Sometimes it indicates a mild infection without fever, especially where there may be infected and enlarged adenoids and tonsils." Reference to the part played by tonsil and adenoid hypertrophy is found in several other reports.

While the pediatricians' reports did not clarify the issue of toxic versus nontoxic pathology, they brought out what in their opinion was the prevalence of infectious colds, but they also reflected a general feeling of uncertainty and desire to find a solution.

It was found impossible to compare the figures relating to the incidence of colds at the Payne Whitney Nursery School with the incidence of colds in the general population at the same age levels. Figures about the latter are not available. Common colds are not considered a communicable disease and, therefore, are not reportable. On the other hand, surveys of large groups of children as found in Public Health Reports are concerned with school children whose ages are well above the two- to five-year-old group. It is also questionable whether such figures would be very helpful. Criteria for the diagnosis of "colds" in school children do not seem very reliable since the diagnosis is, in the majority of the cases, made by nonmedical individuals, and without medical supervision. Under the circumstances it was difficult to compare the data with those obtained in other group studies.

#### GENERAL FINDINGS

**Seasonal Incidence**—The total number of days of absence for colds in the present study showed variations from month to month, and from year to year. To avoid errors due to the noninclusion of week days and holidays, the curves of incidence were plotted in percentile, taking the total number of absence for colds as numerator and the total number of possible days of attendance at school as denominator (see Fig. 49). A similar computation was made for the plotting of a con-

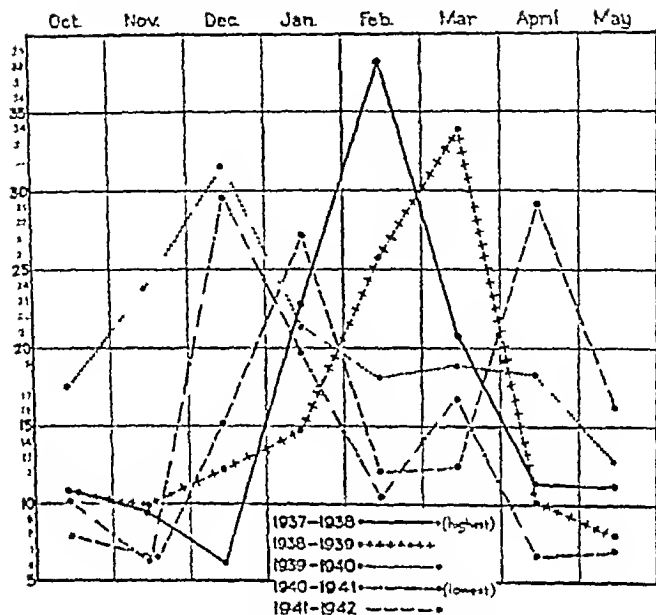


Fig. 49 - Variations in absence for colds, from month to month, for the years 1937 to 1942 plotted in percentile.

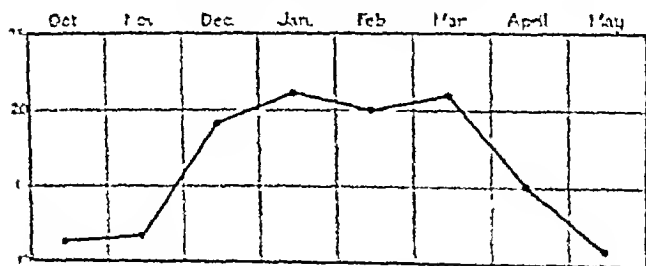


Fig. 50 - Average absence for colds for the year 1937 to 1942 showing absence for colds from month to month.

Figure 50 is a curve covering the five school years 1937 to 1942 (see Fig. 50).

The school year 1937-38 shows the highest incidence, and 1940-41 the lowest incidence

There are also monthly variations, which bring out the cyclic character of cold incidence, with the emergence of peaks, respectively in winter and spring. The position of the peaks varies from year to year, as follows

1937-38 (19 children)	peak in February
1938-39 (19 children)	peak in March
1939-40 (19 children)	peak in December and March
1940-41 (18 children)	peak in December and March
1941-42 (18 children)	peak in January and April

The conglomerate curve (ninety-three children) shows two peaks, respectively in January and March

Since they deal with a small number of children, the curves have little or no statistical value, nevertheless they follow the general pattern of other curves of incidence, plotted from larger groups. This is the case, for instance, of a study reported elsewhere<sup>2</sup>. The peaks for the years 1937-38 and 1938-39 in this study coincide approximately with the peaks of the corresponding years at Payne Whitney Nursery School. As expressed by the author of this report, "It will be noted that the seasonal trend is not wholly consistent, that is, the maximum and minimum periods of colds do not occur in the same month each year."

In this same article a statement was made to the effect that "week-ends and Wednesdays have lower incidence values than the other days of the week," and an attempt was made to interpret the variations of terms of "several psychological factors." This was not substantiated by a computation of absences on first, third and fifth days of the week. The yearly number of absences for colds on these respective days, as well as a conglomerate figure for the five years, was obtained but showed no significant differences between the figures.

**Sex Distribution**—After listing the children in order of frequency of absence for colds, in percentile, as obtained through the method described above, the first nine children for each year were defined as the children with the highest incidence, and the remaining nine or ten as the children with the lowest incidence. In investigating the sex distribution of the children in the two groups, it was found that in the first group, *i.e.*, *highest* incidence, they were distributed as follows

9 children per year, total for 5 years	45 children
Boys	29
Girls	16

In the second group, *i.e.*, *lowest* incidence, they were distributed as follows

9 or 10 children per year total for 5 years	48 children
Boys	17
Girls	31

It is recalled that for research purposes an attempt is made to secure an even distribution of the sexes, and that during the years 1937-42 there were sixty-three children under study at the Payne Whitney Nursery School, of whom thirty-two were boys and thirty-one were girls.

This apparent predominance of colds in boys cannot be checked against other studies, as these are wanting in the literature, medical or psychological. One can only speculate on the various possible interpretations but one deserves serious consideration, namely, the higher frequency of problems of internal tensions in boys, as compared with girls in the preschool age range (anxiety and behavior problems).

**Year in School**—The majority of the forty-five children (first nine each year) with highest incidence are children who were attending nursery school for the first time, as shown by the following figures:

In their 1st year at school	34
In their 2nd year at school	10
In their 3rd year at school	1

This is true whether the child enters nursery school in the first (two to three years) second (three to four years) or third group (four to five years).

In a group of thirty-four children attending nursery school on two successive years, it was found that twenty had a higher incidence of colds (in percentage) during the first year and fourteen a higher incidence during the second year.

**Days of Absence**—The days of absence for individual colds showed considerable variations from child to child (one day to thirty-five). The number of colds in the school year for any one child varied from one to sixteen and the average absence for colds in individual children varied from one to 12.5 days.

#### CHILDREN FROM BROKEN HOMES

While the children coming from broken homes are not the only children subjected to psychologically traumatic experiences such experiences are always present in these children. The removal of the father from the home, however interpreted, is a disruptive element in the emotional adjustment of the child, and it will also be readily agreed that the home conditions prior to the separation are not conducive to creating a happy emotional atmosphere.

**Incidence of Colds**—The yearly absence to day for colds in this group

of children, computed in percentile by the method described above, are tabulated as follows for each successive year spent at school

Boy	CB	25 51 — 9 49 — 35 25
Boy	HR	17 19 — 14 55
Boy	UM	20 16
Boy	FN	51 72 — 19 73
Boy	QB	8 97 — 13 72
Girl	BB	12 89 — 21 79
Girl	DI	21.22 — 25 64
Boy	UR	15 15

The mean total of absences for colds in percentile for all eight children is 19 05 per cent. The mean total for all other children (63 minus 8 children from broken homes, 55) is 15 85 per cent, which does not represent a significant difference, but as pointed out previously, the remaining fifty-five children included some who, for reasons other than disruption of the home, had disturbing emotional experiences. For purposes of comparison, a group of eight well adjusted children, coming from especially happy homes, was selected, and their ratio of absences for colds was computed through the same method, and found to be 9 46 per cent. The latter figure represents a significant difference from the 19 05 per cent obtained in the case of children from broken homes. On the other hand, there are a few anxious children whose health records are among the best. The meaning of these various relations can be analyzed from a more general point of view than that of the broken home children alone, and it is planned further to investigate these relations. However, it has been found convenient to select this special group because of the evidence of gross emotional disturbances among them.

**Physical Data**—All the children in the group were well developed and well nourished. Birth weight, birth conditions, early psychomotor development, and nutrition did not present any abnormalities, except for one boy with congenital clubfoot (also mild skin allergic manifestations), one girl with possible allergic history ("rose fever" at three months) and one boy with mild symptoms of rickets. Six of the eight children had had breast feeding six weeks or less (two of these, none at all) and the other two, respectively three and three and one-half months. In the light of the observations of Grulee and Sanford<sup>3</sup> on the low incidence of infantile eczema in breast-fed children, on the one hand, and the increasing awareness of the relation between allergic manifestations and common colds on the other, this finding should be emphasized. Its psychological determinants and implications also deserve careful investigation.

All the children had had colds before being admitted to school, and none a tonsillectomy. For all, the health record had been good, except for the colds which were variously reported, for the period antecedent

to school attendance, as 'susceptibility to colds—only illness severe colds, etc.' No childhood diseases were reported except whooping cough with a great deal of vomiting in one girl at age three, just before entering school at the time of the parents' separation. One boy was said to have had a "perfect health record" to eighteen months when he began having colds. It was otherwise reported in the history that the parents' separation took place at this time. The history of colds prior to school attendance was generally not reliable enough for definite time relationships to be established as the colds were reported only in degrees of severity and frequency. Poor appetite was reported in two children.

CHILDREN'S HISTORY

attitudes toward other children and adults Whenever possible, efforts were made to enlist the parents' cooperation as regards the child's need for love and reassurance

#### REVIEW OF THE LITERATURE

Most medical authorities agree on the *symptomatology* and *etiology* of the common cold Dochez<sup>4</sup> describes the symptoms as "those of irritation and swelling of the mucous membranes of the upper respiratory tract accompanied by a constitutional reaction from toxic substances absorbed at the focus " He also points to the difficulties of differentiating true coryza from "a hyperemia of the mucous membrane due to noninfectious causes " Filtrable virus and secondary bacterial invasion are generally considered the pathogenic agents<sup>5, 6 7</sup>

There seems to be less clarity on the point of *susceptibility* to colds In discussing prophylactic immunization against colds Dochez<sup>4</sup> observes that "there seem to be factors then in the nature of susceptibility which make it extremely difficult to accomplish any practical results " Similarly, Kneeland<sup>8</sup> concludes, after a survey of various factors "it becomes plain that we do not really understand the general and constitutional factors which underlie susceptibility to colds "

The relations of *allergy* (skin or upper respiratory) to the common cold, though not yet clearly defined, are increasingly emphasized in the literature For instance, Rudolph<sup>9</sup> considers "the prevention of asthma and other forms of major allergy as the ultimate goal in the treatment of frequent colds and chronic coughs of proven allergic nature " However, since allergic colds are very rare in children under five years of age (the younger, the less likely they are to have upper respiratory manifestations, the more likely to have skin allergy)<sup>10</sup> and since the pediatricians have not in our study made a positive diagnosis of upper respiratory allergy, the problem is reduced to the possible existence of relations between *emotional factors* and frequency of non-allergic colds In this area the literature does not offer many clues

MacAuliffe, Goodell and Wolf<sup>11</sup> relate local vasomotor changes taking place in the erectile tissue of the nose following various emotional stimuli The removal of the coryza sufferer from daily stresses and frustrations during the acute phase lessens both pain and secretion They substantiate the observations of Fenton<sup>12</sup> who describes the state and appearance of the nasopharyngeal mucosa in relation to fear, severe shock (also pain elsewhere in the body, sudden fright), anger (also excitement, heavy eating or drinking) and sexual stimulation In particular, congestion and turgidity are associated with anger, a point to be emphasized since a boggy and hyperemic mucosa is considered favorable to pathogenic invasion

In the psychosomatic literature Saul<sup>13</sup> reported a series of fifteen patients with frequent colds before analysis (initiated for the treatment



of various neurotic symptoms, whose colds were either markedly reduced or totally removed after the analysis. In nine cases it was possible to note that the colds "occurred in situations of frustration of strong, mostly unconscious receptive demands with more or less repressed rage." Similarly French and Alexander<sup>14</sup> brought out relations between asthma attacks and emotional conflict situations in patients. It is reported that these patients had an early history of frequent colds.

#### SUMMARY AND CONCLUSION

A survey of the records of sixty-three children (thirty-two boys and thirty-one girls) admitted to the Payne Whitney Nursery School from 1937 to 1942 was initiated to determine whether relations between frequency of common colds and emotional states could be observed. Among the children with the highest ratio of absences due to colds were found the eight children from broken homes, a large number of children with emotional stresses due to other causes than home disruption and a few children apparently free from such stresses. Conversely there were a few children who while presenting emotional problems were relatively free from colds. Whether accompanied or not by signs of toxicity, the colds were reported by pediatricians to be of the infectious type, and no positive diagnosis of allergic cold was made. There were more boys than girls in the group of children with the highest ratio of absence for colds.

In the case of the eight children from broken homes, all with high incidence of colds, there was evidence of gross emotional disturbances in the nature of anxiety and frustration. It is planned further to investigate and analyze the total data and evaluate the interrelations of psychosomatic factors, but it is already apparent that in some cases internal tensions due to psychologically traumatic situations may be operating among other factors contributing to individual susceptibility to colds.

volunteered the information that he and his wife were on the verge of a separation and that the home had been in a state of turmoil for the past year. The mother, an exponent of progressive education, believed in making the boy face reality. Discovering that he was afraid of lightning, she made it a practice to hold him at the window "to see the pretty lights and hear the big 'boom'." On one such occasion the storm was unusually violent, and lightning, to the accompaniment of a deafening peal of thunder, struck and shattered a nearby tree. The child became speechless with fright and the next day commenced to stutter.

A tense, worrisome home environment may also act as a precipitating factor in stuttering, e g

P E, aged three years, was brought to the clinic with the story that his speech had been slow in developing and that he had recently begun to stutter. The mother volunteered the further information that he would play only with smaller children and that older children "made him nervous." When older children came near him, he would cry, put his hands to his ears, and run away. He slept poorly and frequently wet the bed. In the clinic he was observed to be apprehensive and fearful that the other children would strike him. He screamed when the clinician touched him, whimpered a great deal, and often glanced to one side as if he was afraid of something.

The family history disclosed that the father, a writer, was temperamental and worrisome. He was easily upset and frequently became depressed. His whole family was said to be "high strung" and emotional. One uncle and two cousins had found it necessary to consult psychiatrists at various times because of phobias, "nervousness," and inability to continue in their respective jobs. The patient's mother was also highly emotional and tense. The maternal grandmother, who lived with the family and was in close contact with the child, was characterized as a "prize worrier and nagger." The two women were incompatible and frequently quarreled. In an effort to get away from the grandmother, the patient's mother at one time stayed several weeks in a "Seven-Day Adventist" sanatorium, where she had complete peace "because my mother couldn't follow me there." She admitted that the home atmosphere was charged with tension and emotionalism that frequently led to quarrels and outbursts of temper.

The child apparently received very little attention except from the grandmother. Despite the admitted parental instability and its pronounced effect on the home environment, the patient's mother could find no explanation for the child's personality maladjustment and the onset of his speech disorder except the fact that his grandmother "fussed" over him too much.

Further observation inevitably leads to recognition of the fact that the severity of the symptomatology is often directly proportionate to the tension and anxiety generated by the particular environmental situation. Stutterers are often able to talk without the slightest hesitation, repetition or other disturbance in the stream of speech when they believe themselves to be alone. Some will stutter only in the presence of their superiors or only in the classroom. In general those situations which are anticipated with anxiety, because of their emotional signifi-

cance to the individual, will invariably accentuate the speech difficulty. Conversely, factors which tend to decentralize or remove the focus from the given individual, such as recitation in unison and singing in a group, will make for comparatively easy and smooth flowing speech. The particular speech content is extremely significant as a potential tension and anxiety producing element. Discussion of certain topics such as relationship to one's parents and sexual adjustment will also lead to exacerbations of the symptom. An analysis of the situations which make for increased speech difficulties will often provide valuable leads to the source of considerable anxiety which may be utilized therapeutically. A case in point is that of a young man who began to stutter at the age of twenty-four.

logic changes as the *cause célèbre* of stuttering. Such studies apparently dismiss the already known psychosomatic interrelationships, for the results are offered without adequate description of the emotional state or psychopathology existent at the time of the examination.

Stemming from such incomplete studies are such untenable statements as the following: "Although the larger quantity of sugar in the blood (in stutterers) may be the result of emotion, it might be expected that the body would make adjustment to the constant fear or embarrassment states of the stutterer." No statistically significant alterations in the postulated biochemical cause are demonstrated in the same individual following a "cure" of his speech difficulties. In view of the numerous forces constantly operative within the stutterer's personality, it appears that only those research programs which study the total personality, correlating changes that occur in the physiologic plane with those that occur at the level of highest integrative functioning, can add materially to our knowledge of stuttering.

With this in mind, studies are now under way which strive for simultaneous or correlated examinations, including neuropsychiatric evaluation, blood determinations, electroencephalography and objective personality studies. The preliminary findings are detailed below.

**Neurological Examination**—Neurological examination of the typical stutterer does not reveal any evidence of peripheral neuromuscular involvement such as would be caused by lesions of the seventh, tenth and twelfth cranial nerves or their nuclei, nor do we find the characteristic dysarthria or disturbances in articulation related to weaknesses secondary to supranuclear lesions. Coordination tests involving rapid, rhythmic, alternating movements, or tests calculated to demonstrate intention tremors, do not reveal evidence of cerebellar asynergia. It is true that many stutterers demonstrate motor awkwardness and clumsiness in the performance of skilled mechanical acts, but this is not a cerebellar type of incoordination.

The most common findings are those physiologic disturbances indicative of tension and anxiety: cold, wet palms and soles, vasomotor instability with a rapid, labile pulse, and occasional adventitious movements such as tics or twitches, especially of the face. Hyperreflexia is not uncommon but this is ordinarily equal on both sides. Rarely are pathological reflexes elicited, and then usually only where there is a history of trauma or other involvement of the central nervous system. The purposeless, jerky, irregular movements of the body—the so-called parakinesias—which frequently accompany stuttering speech may be viewed as an expression of the tension which "overflows" into centrifugal manifestations.

**Blood Determinations**—Studies showing that *leukocytosis* often accompanies various emotional states when no infectious process or structural changes can be found to account for it, suggested similar

laboratory studies on stutterers. Accordingly, white blood cell counts were taken under basal conditions following the technique described by Milhorat, Small and Diethelm. In a series of fifty initial counts taken on stutterers who were in good physical health, eighteen patients, or 36 per cent, showed white blood cell counts over 10 000. Six of these cases had counts over 12 000 and one patient who was obviously psychotic and on the verge of panic had a count of 17 500. Psychiatric hospitalization was necessary in her case. With a decrease in anxiety, the frequency and intensity of speech difficulties diminished and the counts returned to within normal limits. In a few particularly unstable individuals the counts fluctuated with corresponding changes in their emotional state. However, it must be remembered that not all patients with intense anxiety show a leukocytosis, even though they may experience other physiologic changes associated with anxiety. In the great majority of patients with elevated white cell counts, the pulse rate was over 90 per minute and approximately two thirds of the total number of patients had wet palms. Three of the patients fainted following the pin prick of the finger.

population at large. A number of these pathologic records have been repeated and verified. Those patients with obvious involvements of the central nervous system or who gave a history of epilepsy in the immediate family were excluded. Thus, two patients were not included in the figures because one gave a history of convulsions earlier in life and the other has a brother who has been subject to fits.

The type of pathological record is not characteristic but varies from case to case. Irregular, low amplitude, fast waves were often seen, with the irregularity increased at times by a two-minute period of hyperventilation. Other pathologic records showed frequent slow waves, usually five to seven per second, especially in the frontal and parietal areas. No particular difference in cortical activity between the two cerebral hemispheres was noted. The fast, irregular, low amplitude waves seemed to correlate with the existence of marked muscle tensions.

The electroencephalogram is a most sensitive indicator and is influenced by numerous factors which are difficult to estimate, such as the emotional state, thinking processes, anticipating movements and muscle tensions. In view of these facts, studies on a small number of stutterers during speech which are purported to show "waves in the tracings from the two hemispheres out of phase and often obliterated" compared with normals, must be accepted with great caution.<sup>8</sup> A proper control group would not be so-called normals but other individuals with anxiety states who do not stutter. The ideal experiment would be to compare records in a stutterer before and after a "cure" of his speech difficulty. Repeated studies should be performed on the same individual correlating the brain wave patterns with his emotional state as well as the many other factors known to influence the form, amplitude and frequency of the waves.

#### THE CONSTITUTIONAL BASIS OF STUTTERING

Despite the known physiologic changes in the blood and the electroencephalogram, we are still in doubt as to the exact mechanism that underlies the instability of the stutterer, but evidence strongly suggests the presence of some constitutional factor which predisposes the individual to emotional imbalance in general and to stuttering speech in particular. It also appears to predispose him to general psychomotor disorganization, since stuttering children are observed to be more awkward and less adept in acquiring motor skills than the so-called normal child. This observation has been corroborated in a study, made by Berry,<sup>4</sup> of the developmental history of 500 stuttering children as compared with 500 normal children. She found that the children who stuttered were definitely retarded in acquiring motor skills. They were retarded in learning to walk when compared with the nonstuttering children, and also "showed a serious retardation both

in the initiation of speech and in the development of intelligible speech."

Thus, in the stutterer we appear to be dealing with a special type of individual, the stutter-type<sup>6</sup>—an individual who from birth is a variant.<sup>5</sup> (His variation appears to be on an hereditary basis since over 65 per cent of patients show a family history of stuttering, however the influence of early environmental situations on the developing personality should not be discounted.) Such an individual acquires a keen sense of inadequacy early in life, undoubtedly even before the appearance of the stuttering symptom. Psychiatric interviews elicit childhood histories replete with nightmares, fears, enuresis, nail biting and unhappy experiences. They also reveal that tendencies to asocial behavior, shyness and seclusiveness were evident early, but since the onset of stuttering was almost always before six years of age the patients relate these tendencies to embarrassment about their stuttering speech. A characteristic history is that of a young man, aged thirty-one years, recently seen in the clinic.

during which interval he became a successful commercial artist. With impending induction into the Army, however, his tension and anxiety increased markedly and there was a recurrence of his speech difficulty

J B stuttered since the age of four, following a scare by German airplanes. He came to this country from Poland at seven years of age, and his stuttering increased in the new school situation. He was always shy and seclusive, and it was necessary for his twin brother to push him in all activities. As a child, he had frequent anxiety dreams, bit his nails, and in general felt insecure. He was troubled by occasional enuresis up to eight years of age. He was first seen in the clinic several years ago, at the age of twenty, and under treatment his speech improved considerably. However, he has continued to be troubled by various neurotic symptoms which his impending induction has greatly exacerbated.

Military service in most cases increases the stutterer's anxiety and exacerbates the speech symptom.

S L., aged twenty-three years, was first seen in the clinic following medical discharge from the Army. He gave a history of having stuttered since the age of four and alleged that the speech disorder had grown steadily worse in the last few years. Early in 1943, he was inducted into the Army in spite of his stuttering. Under the strain of military service, his speech became very much worse and he began to complain of other neurotic symptoms. Because of his condition, he was sent to an Army hospital for observation and was eventually discharged. When seen in the clinic he complained of palpitations of his heart, "constriction" in his throat, and excessive "sweating," and his speech was characterized by frequent and severe blockages.

An accident will often increase the severity of a stutterer's speech disorder.

R L., aged seven years, began to stutter when he first started school at the age of five. However, his hesitations were slight and had almost completely disappeared when he met with an accident in school. While playing in the school yard, he was struck between the eyes by the seat of a swing. Both eyes became black and a lump formed on the child's forehead, however, x-rays failed to disclose any serious injury. Following the accident he began to stutter severely and to jerk his hands and feet in an effort to get words out. At times he was completely speechless, and because of the severity of the blockages the school teacher advised the child's mother to bring him to the clinic.

#### SOMATIC SYMPTOMS

The most common somatic symptoms observed in the stutter-type individual, in addition to speech difficulties, are wet, cold palms, palpitations, pounding or irregularity of the heart beat, a tightness in the cervical musculature, and a sinking sensation, tightness or emptiness in the abdomen. Well over 75 per cent of the patients studied intensively had two or more of these symptoms. Sleep disturbances are much less common and then usually the individual complains of trouble



in falling asleep or being awakened by disturbing dreams. Tension headaches are infrequent

#### RORSCHACH (INK BLOT) TESTS

Psychiatric interviews were supplemented by Rorschach (ink blot) tests adapted for group purposes following the method recommended by Dr. Harrower Erickson.<sup>6</sup> The tests were given for the purpose of obtaining a more objective evaluation of the patient's emotional status, particularly evidence of neuroticism. In the test it is assumed that the individuals most likely to give certain types of responses spontaneously will select similar answers in a multiple-choice situation.

Each card (ink blot picture) is presented together with a series of ten answers from which the subject makes a choice for the best description of the whole blot or any part of it. If none of the suggested answers satisfies the individual he may then write in an alternate answer. The scoring is done with a key which scores each response as a digit ranging from 1 to 10. Alternate answers are scored A. The lower digits indicate good or more normal responses. For example No. 2 stands for the popular animal response to a card. No. 6 indicates anatomical answers. No. 7 often depicts anxiety, and so on. Responses with a digit value of 6 or over, or alternate (A) answers are considered poor responses. Patients who score four or more poor answers usually have a moderately serious emotional maladjustment.

In a group of thirty-three stutterers, ten patients, or thirty per cent, showed scores with four or more poor answers. This is to be compared with Harrower Erickson's figure.

Thus it is obvious that the stutter-group shows an emotional instability far above the normal range. Individual Rorschach tests given to a number of those patients whose scores were below 40 often showed evidence of a neurosis in the form of definite color shock with primary color responses. One patient in the "below 40" group showed two failures (no response to a card) which is decidedly abnormal.

**Results in the Case of "Cured" Stutterers**—Three "cured" stutterers were also examined. One is a lawyer who is active in court and speaks on the radio without any evidence of stuttering, another is a New York City high school teacher who lectures without stuttering, and the third is a successful artist who also speaks without any difficulty. All three showed moderately severe anxiety, with wet hands and tachycardia. One complained of "inner restlessness," another of being unable to relax, and the third—the artist—felt a "sense of inner agitation." The following are the group Rorschach scores which indicate the persistence of emotional instability.

	Card No										Total
	I	II	III	IV	V	VI	VII	VIII	IX	X	
Lawyer	7	8	1	2	2	2	8	2	9	10	51
Teacher	10	7	8	10	2	9	1	2	3	3	55
Artist	5	7	2	6	2	2	8	5	3	2	42

Thus it seems apparent that we may have a so-called "cure" of stuttering with the underlying emotional conflicts seeking another outlet in the form of other neurotic symptoms. Two other "cured" stutterers showed only a tendency to anticipate with anxiety, but otherwise they were relaxed and able to work successfully. Their Rorschach scores were well within the normal range. Scores are as follows:

	Card No										Total
	I	II	III	IV	V	VI	VII	VIII	IX	X	
Subject No 1	5	3	2	5	2	2	1	2	6	2	30
Subject No 2	5	6	1	5	2	3	2	2	3	2	31

It is obvious that no conclusions can be drawn from the small number of "cured" stutterers examined so far. But the fact is apparent that individuals may dissociate their stuttering speech from an underlying neurosis and have no speech difficulty despite the presence of an anxiety state.

#### TREATMENT

Since stuttering speech is but a physical manifestation of an underlying personality disorder in a constitutionally susceptible individual, the treatment should be composite in nature. It should be directed to—

ward overcoming the stutterer's inherent limitations and his specific fears and anxieties and should strive to develop a more mature and stable personality as a whole. Adequate treatment should include therapy of a medical social psychiatric and reeducational nature.

For therapeutic purposes, we distinguish two phases of stuttering the *primary*, and the *secondary*. The primary stage of stuttering is the initial phase of the disorder, before the child has become acutely aware of the penalties attached to it and before he has developed anxiety symptoms and other characteristic personality deviations. The physician should in no instance disregard this primary phase of stuttering on the theory that the child will "grow out of it." This happens in less than 10 per cent of all cases.

**Treatment in the Primary Stage**—Treatment in the primary stage of the disorder is largely a matter of *treating the parents* and through them, removing unfavorable environmental influences. The aim is to arrest the disorder and to prevent its developing into the secondary stage. A medical examination should determine the general health of the child, and a therapeutic regimen embodying the following points should be worked out with the parents.

The precipitating factor if known should be eliminated or its influence counteracted through psychotherapy or other suitable measures.

The child who stutters is "high strung" and sensitive and overreacts to almost all stimuli. In other words he is *different* from and must be treated *differently* than the average child. Parents should take this into consideration especially in matters of discipline. Discipline should be firm and consistent but never harsh.

Encourage the child to do everything *slowly and easily*. The parents should strive to inculcate within him a sense of coordination and rhythm. They should encourage him to play simple games which require accuracy of movement and muscular coordination. Games or family contests in which the emphasis is on talking, playing and working slowly and easily are excellent ways of improving the child.

Watch the child's general health. See that his diet is well balanced and contains adequate amounts of all the vitamins especially vitamin B<sub>1</sub>. See also that he gets enough sleep. Fatigue will accentuate his speech difficulty. A nervous child needs more than the ordinary amount of rest and relaxation.

Begin to strip off the child's reaction to the habit of stuttering before he begins to state a question to you in form of a question. Encourage him to give answers in form of statements which require no further explanation or discussion.

Any tendency toward overreaction to the habit of stuttering should be discouraged. At the same time, the child should be encouraged to express his feelings and emotions.

Do not make the child feel that he is "different" from other children.

ing his speech The parents should exemplify good speech by speaking slowly and deliberately A tactful suggestion—"Let's try to talk slowly, Mother doesn't hear so well today"—will usually produce better results than making the child stop and repeat any particular word with which he has had difficulty

Strive to build up the child's self-confidence Concentrate on his good points and special abilities rather than on his speech disorder and other disabilities Encourage him to mix with other children and to invite them into his home

Enlist the cooperation of teachers and playmates so that the school atmosphere may be made as sympathetic as possible for the child and so that other children do not mimic him or laugh at him when he stutters Encourage him to talk, both at home and at school, but never *make* him do so

Never punish or ridicule the child when he stutters Never make him feel that he is "different" or the object of pity Treat him with unobtrusive sympathy and understanding Parents should let him know that he is secure in the possession of their love

Treatment in the Secondary Stage—The adolescent or adult stutterer is too much concerned with what others think of him He is ordinarily quite sensitive to criticism and his feelings are easily hurt He will tend to accumulate these hurts within himself and picture the world as a hostile, critical, unsympathetic environment He must be taught now to develop an "I don't care" attitude He should repeat to himself, "I don't care if I do stutter," because the less he cares the less trouble he will have He should be encouraged to socialize more freely and not hesitate to allow others to observe that he stutters

The real problem is not speech at all, but *the stutterer's attitude toward the world*—his fear that he won't measure up, a lack of self-confidence and a feeling of inferiority One way of increasing his self-assurance is to concentrate on making his appearance as pleasing as possible, dressing neatly and attractively, smiling pleasantly and being thoughtful and considerate of others A hobby at which the stutterer can excel will often give him a greater feeling of self-esteem, and so help to compensate for his inadequacy reactions

Anticipating difficulties with worry and anxiety increases emotional tension and depletes the individual's energy reserves to the point where he is less fit to meet the impending difficulty As soon as the stutterer finds himself getting anxious about a recitation he must give tomorrow, he should make a conscious effort to substitute other more constructive thoughts In the beginning this will be difficult because it takes practice and repetition to break a long-standing habit, but it can be done

The stutterer should try to get a mental picture and feeling of himself in a *calm, relaxed state* and then try to cultivate such relaxation

and repose as his usual pattern. When he talks he should not think about his speech but should concentrate on feeling as relaxed as possible. "Go limp loosen up get the feeling of being a rag doll. To get the feeling of relaxation in his throat and jaws, open the mouth wide and yawn. Try to remember how this feels and when those muscles begin to tighten up again take a deep breath open the mouth wide and yawn. The stutterer should practice this until he can learn to release these tensions as soon as he becomes aware of them.

The stutterer should learn to talk and to do everything slowly and effortlessly. "Slow Easy" sums up a philosophy that every stutterer should adopt as his own. The stutterer should constantly keep in mind that *he does not suffer from a speech defect but rather from a fear of speaking under certain conditions*. Reading aloud to others may be practiced at the beginning but should soon be supplemented by *speech practice* in an environment which recreates as nearly as possible the conditions under which he has difficulty. Thus, he should practice talking to someone particularly to a group of people. At first he should select a sympathetic and encouraging group who will give him the confidence he needs. Spontaneous talk should be encouraged such as in a discussion group concerning current events. The stutterer should strive to speak slowly easily freely setting up a smooth flowing rhythm and concentrating on feeling relaxed and calm. Gradually he will be able to carry this same ease of speech and relaxed feeling into the outside world.

the individual to gradually increasing pressures. Thus he in time develops stability and emotional control sufficient to enable him to face the everyday situations of life without becoming disorganized. Treatment proceeds with encouragement, reassurance, suggestion, sympathetic understanding, and a slow, easy informality. It is supplemented by social activities through the medium of clubs, group singing, dramatics and public speaking.

### CONCLUSIONS

1 Stuttering speech is not a disease but a symptom of an underlying personality disorder. The most common psychopathological symptoms observed are those related to tension, anxiety and emotional immaturity.

2 Physiologic changes, such as elevated white blood cell count, vasomotor instability, hyperreflexia and pathological electroencephalograms, are to be viewed as associated findings related to the psychobiologic status of the individual and not as etiologic factors.

3 Over 65 per cent of patients show a family history of stuttering, but the influence of early environmental situations should not be minimized. Psychiatric interviews reveal numerous evidences of personality disharmony in childhood, with tendencies to asocial behavior, shyness and seclusiveness developing early in life.

4 Rorschach tests reveal evidence of marked emotional instability in approximately 30 to 40 per cent of stutterers.

5 Successful treatment demands a pluralistic therapeutic approach.

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## PHYSIOLOGIC AND PSYCHOLOGIC CONSIDERATIONS OF DELIRIUM

JOHN ROMANO, M.D.\* AND GEORGE L. LACEL, M.D.†

It is unfortunate that many nurses, students and physicians use the term 'uncooperative' or 'stupid' in describing certain seriously ill patients who are unable to present details of their illness or who fail to follow commands during examination and during the administration of therapy. We have noted that a great many of these so-called uncooperative patients are experiencing disturbances in consciousness. These patients find themselves in the absurd position of being described as stupid or uncooperative when the actual state of cerebral physiology prevents them from understanding what is said to them, much less performing logically or efficiently from that point. Essentially these patients may be experiencing varying degrees of a delirious process.

It is not unexpected that many of these patients are not recognized as being delirious since the traditional concept of delirium has emphasized behavior disturbances of exaggerated degree. This usually means that the diagnosis of delirium is made when the patient creates an acute disturbance. Actually delirium is a syndrome in which the basic psychologic symptom is a disturbance in the level of consciousness which in turn is dependent upon underlying physical disorder. Thus it may occur in patients with no pre-existing structural cerebral disease and may be associated with drug intoxications (alcohol, barbiturates and others), febrile states, or circulatory and metabolic disturbances. It may also occur spontaneously or because of the aforementioned provoking factors in patients with pre-existing cerebral disease.

## PSYCHOLOGIC SYMPTOMATOLOGY

Fundamentally, the psychologic symptomatology is based upon an increased fluctuation in the level of awareness. For example, the signs of delirium include sleep disturbances with increased frequency of frightening dreams and nightmares, misinterpretations of people, objects, shadows and odors, increased motor restlessness, and anxiety expressed through irritability or through somatic concern. Essentially these symptoms are indicative of a decreased ability on the part of the patient to distinguish between reality and phantasy. Frequently in this stage the patient remarks anxiously, "I don't know if I dreamed these things or not." The patient may progress to the stage where his experiencing of reality is more or less completely distorted, where he utilizes delusional thinking, where he experiences sense deceptions and considerable anxiety.

In some instances behavior may be characterized by considerable motor excitement and the total picture may assume clinical proportions of such intensity that he becomes a custodial problem in the home or in the hospital. More frequently one observes somnolent and stuporous developments, in which the distortion of reality, the delusional thinking, the anxiety, and the sense deceptions are not overtly expressed yet are readily revealed by more direct examination. Urinary and fecal incontinence and inability to feed one's self are common manifestations in this phase. Concomitant with the fluctuations in the level of consciousness, there are changes in muscular coordination. As the delirium increases in intensity one notes restlessness, irregular movements, groping, pointing, grasping, picking at bedclothes, clonic and tonic movements and torsions.

## DIAGNOSIS

It should be emphasized that the state of consciousness is a sign as objective as the contour of the chest, the color of the skin, or the palpability of the liver. While depression of consciousness to stupor or coma is readily apparent, diagnosis of lesser changes in the level of awareness requires more direct examination, which may be incorporated in the course of routine history taking and examination. This includes observations of the patient's ability to attend to questioning and examination, the degree to which this attention fluctuates, the speed and accuracy of responses, and the accuracy of orientation. Usually there is no need for the patient to be examined in detail by the traditional mental status examination. Certain simple tests may be used to confirm the impression gained through eliciting the historical data and observing the patient's ability or inability to attend to the task.

For example, we have found the *serial subtraction of numbers* the most valuable test. After or during the physical examination the pa-



tient is asked to subtract three or seven serially from a given figure (usually 100). The test is not intended to measure the patient's arithmetical ability as much as it tests attention, concentration, endurance, and utilization of concepts without sensory guidance. The examiner notes the length of time necessary to complete the test, the number of arithmetical errors and where they occur in the series, whether there is repetition or a stereotyped pattern of error, the emotional reaction of the patient, the presence or absence of hesitation, obvious heightened effort or evasion. Long before arithmetical error may be manifested the patient may betray his decreasing ability to perform the task by heightened effort, increase in total time of the test, frequent hesitation or questioning, requesting a new start or becoming irritable and depreciating the test and the examiner. In other words, the arithmetical errors when the total number is less than three, is of less importance than the manner in which the patient performs the test. The validity of the test, obviously, is dependent upon at least a grammar school education.

tional feelings This is most clearly seen in delirious alcoholic patients, where the deeply repressed homosexuality is portrayed in an exaggerated manner

There exist also considerable individual variations in the ease with which disturbances in consciousness develop under comparable circumstances Every practicing physician knows of patients who become delirious easily, with mild elevations of temperature or with small doses of sedative drugs It is obvious that while the variations in the content of behavior depend largely upon personality structure, variations in the ease of development of disturbances in consciousness are more dependent upon the premorbid physiologic integrity of the central nervous system

#### PHYSIOLOGIC BASIS OF DELIRIUM

These formulations bring us to a consideration of the fundamental physiologic substratum of delirium If the total behavior of the delirious patient may be interpreted as being due to a release of higher cerebral function, what physiologic evidence may be presented to support such an hypothesis?

The sensitive metabolic needs of cerebral tissue and particularly of the cortex are well known Serious disturbances in functional cortical integrity would seem likely in the course of the major physiologic derangements accompanying many of the more serious disease processes These physiologic derangements may result ultimately in disturbances of (1) transport or delivery of oxygen, glucose and other essential food stuffs and intermediaries to the brain, (2) depression or alteration in cerebral intracellular metabolism, or (3) a combination of both

Methods of studying human cortical functions are limited, but the knowledge that the electrical activity of nervous tissue closely parallels its functional integrity has made available a similar approach in humans The *electroencephalograph* offers a method of studying the electrical activity of the human cortex Gerard and his co-workers<sup>1</sup> have presented evidence to show that the electroencephalogram represents the synchronized electrical activity of the individual neurons Some of the major factors determining these neuron potentials are the metabolic activity of the cell, the cellular membrane charge, and the nature of surrounding fluid medium The resultant electrical activity may be modified by, but is not solely determined by, influent nerve impulses Changes in wave frequency, form and, within limits, of amplitude induced by applied agents may be considered in terms of the individual neuron beat. Regularity, on the other hand, may be more readily interpreted in terms of a synchronizing mechanism There is further evidence to suggest that the synchronizing process may be controlled or enhanced by "pace-making" cells, which set others off



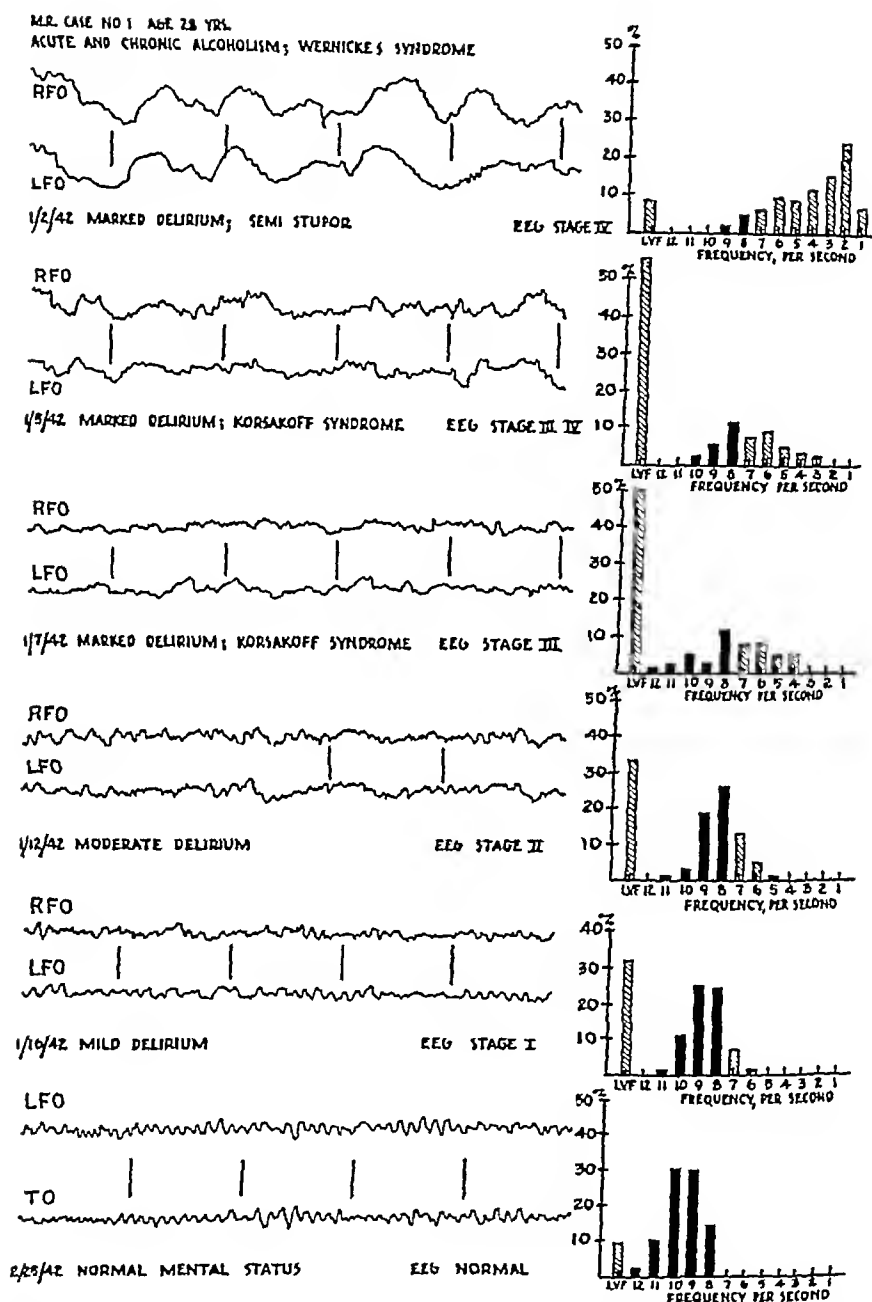


Fig 51—Electroencephalographic data during spontaneous recovery from delirium during acute and chronic alcoholism and Wernicke's syndrome in a twenty-eight-year-old woman

of the electrical abnormality and the primary psychologic symptom in delirium, i.e., the disturbance of consciousness. There was little or no correlation, on the other hand, with the more personal

aspects of behavior, namely, the character and expression of anxiety, the content of thought, or the nature of sense deceptions.

Preliminary observations of total cerebral oxygen uptake using Ferris' method of measuring cerebral blood flow<sup>4</sup> have indicated that there is a reduction in total cerebral metabolism during delirium. These data, however, are as yet insufficient to permit detailed interpretation.

Figure 51 illustrates the typical electroencephalographic changes during the course of spontaneous recovery from delirium experienced during acute and chronic alcoholism and Wernicke's syndrome by a twenty-eight-year-old woman.

At the time of the first examination (January 2, 1943) the patient was stuporous, mumbled incoherently, and was completely incapable of responding to any formal testing. Three days later she was no longer stuporous, but was comatose, lethargic, disoriented, misidentified people, confabulated freely, showed marked fluctuation in attention, and rambled from one topic to another through vague associations as in a dream. On the third examination (January 7, 1943) she was still disoriented, confabulating, confused, inattentive, but now was able to read, though with many errors and without comprehension or memory. On the fourth examination (January 12, 1943) the patient was much more alert and almost correctly oriented. She felt as if she had awakened from a long and disturbing dream. She was able to subtract serially, but with a number of errors. She still confabulated some. On January 16, 1943 (fifth examination) she was correctly oriented and revealed only minor defects. The last examination (February 25, 1943) was done after the patient had been back to work for two weeks. The mental status was completely normal.

correction of known physiologic derangements offers additional support for this concept. With delirium induced in normal individuals by oxygen lack, alcohol and certain toxic materials, in which there is every reason to believe that the noxious factors depress or derange intracellular cerebral metabolism, it has been possible to demonstrate significant shifts in the frequency of the brain waves very early, even

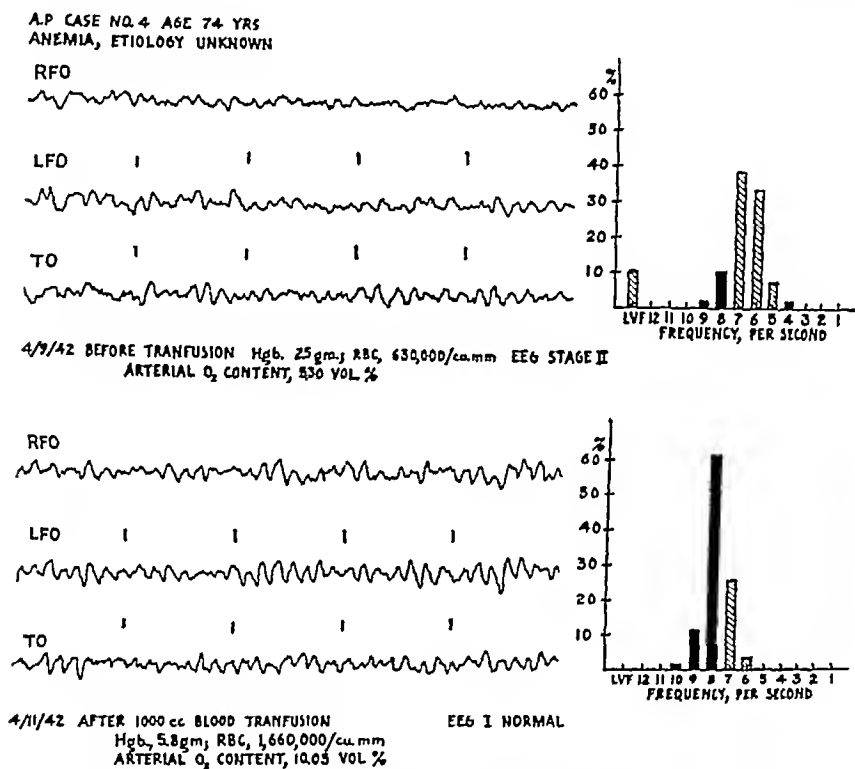


Fig. 52—The effect of blood transfusion on the electroencephalogram during delirium due to severe anemia

when changes in higher intellectual function could be elicited only with difficulty. These data, along with the more gross correlations established in clinical delirium, convince us that the electroencephalogram may be used as an indirect index of cortical metabolism. The preliminary observations on total cerebral oxygen uptake, a relatively gross procedure, also support this view.

#### IMPLICATIONS IN TREATMENT

These studies thus provide a more rational basis for the management of the delirious patient. Therapy must be considered from two aspects, physiologic and psychologic. Obviously the prime objective is to restore cortical metabolism to normal. This involves not only correction of the basic physiologic derangement, but also the avoidance of superimposition of new factors. The noxious factors involved in any

delirious reaction are likely to be multiple and it is not always possible to establish which of these is the most important. Clearly this involves a good understanding of the primary disease process.

**Specific Therapy**—The conditions most frequently encountered and most readily accessible to specific therapy include anoxemia due to pulmonary or cardiac disease, fever and toxemia due to infections, dehydration and disturbances in electrolyte balance due to abnormal fluid loss, anemia, metabolic derangements in uremia, diabetes, Addison's disease, hypoglycemia, nutritional deficiency and Cheyne-Stokes respiration. Superimposed upon these conditions may be the effects of drugs, particularly barbiturates, bromides, digitalis and sulfonamides, where adequate steps for their elimination must be instituted. Patients with pre-existing structural cerebral disease are less apt, for obvious reasons, to respond to such measures.

sion at the bedside, and when explanations of procedures are given to the patient they should be couched in reassuring terms and not in frightening or scientific terminology. With inadequate bedside supervision restraint may be necessary. We have found a low bed to be preferable to the use of sideboards.

### SUMMARY AND CONCLUSIONS

1 The diagnosis, understanding and management of delirious patients constitutes an important aspect of the practice of medicine.

2 Essentially, delirium is a psychotic syndrome in which the basic psychologic symptom is a disturbance in the level of consciousness which in turn is dependent upon derangement in cortical metabolism secondary to physical disease.

3 Psychologic and electroencephalographic studies in induced and spontaneous delirium have established a correlation between the level of consciousness and the electrical activity of the brain.

4 The content of thought, sense deceptions and emotional behavior of the patient are dependent principally upon the premorbid personality structure of the patient.

5 Awareness of the fundamental psychological symptom will enable the physician to diagnose correctly many cases of the delirious process in its various degrees.

6 Intelligent treatment is based upon understanding and correction of the factors which have disturbed cortical metabolism. In addition, wise and comforting bedside management will shorten the delirium and prevent recurrence.

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effectively about 1817 in his medical practice and published extensively on its suitability for certain types of patients. Esdaile, through Elliotson's writings, became so interested that he succeeded in having a government hospital built in India primarily for the use of hypnosis, where he extended its use to all types of patients, especially surgical.

In 1841, James Braid, an English physician who bitterly opposed "mesmerism" as it was then called, was induced to make a physical examination of a mesmerized subject. He recognized both the validity of the phenomenon and its psychological character, with the result that he coined the terms "hypnosis" and "hypnotism" and initiated the first scientific studies of hypnosis as a psychological condition of extensive significance medically and scientifically.

Since then, clinicians first and psychologists later, among them many outstanding scientists, have contributed increasingly to a better understanding and utilization of hypnosis as a scientific tool and as a medical procedure of immense value for certain types of patients. Particularly has interest been developing rapidly during the last twenty-five years among psychiatrists and psychologists. During the last fifteen years there has been an increasing wealth of publications dealing with the effective use of hypnosis in the fields of psychiatry and experimental psychology.

Regrettably, however, there is still a persistence of outmoded ideas and concepts of hypnosis which vitiate experimental studies and therapeutic efforts. For example, some psychologists are still publishing studies based upon techniques and psychological concepts belonging to the nineteenth century, and some medical men still employ it for direct symptom relief rather than as an educative procedure for the correction of personality disorders.

As yet, the scientific study of hypnosis is still in its infancy despite the development of a healthy, intense interest in it as a scientific problem of merit. There is still lacking an adequate general appreciation of the need to integrate hypnotic studies with our present-day concepts and understandings of personality, of inter- and intra-personal relationships and psychosomatic interrelationships and interdependencies.

#### GENERAL QUESTIONS

In any discussion of hypnosis, certain general questions arise concerning who may be hypnotized, the possible detrimental effects of hypnosis, its possible antisocial use, the nature of the hypnotist-subject relationship, the controllability of the hypnotic state, the relationship between hypnotic sleep and physiological sleep, and the possibility that hypnosis may crystallize or precipitate abnormal or pathological conditions in subjects that otherwise might have remained indefinitely dormant.

Reply to these questions, because of space limitations, must necessarily be brief and dogmatic and the reader is referred to the bibliography of this paper for the references upon which reply is based.

Briefly there are no injurious or *detrimental effects* upon the subject other than those that can develop in any other normal interpersonal relationship. Hypnosis cannot be used for *antisocial* or criminal purposes although most subjects can be induced to commit make believe or pretended crimes but pretenses should not be accepted as realities. The *hypnotist subject relationship* is entirely one of voluntary cooperation and no subject can be hypnotized against his will or without his cooperation, the hypnotist subject relationship is analogous to that which exists between physician and patient, lawyer and client, minister and parishioner. Furthermore a subject can be a hypnotist and a hypnotist can be a subject and they can work with each other in alternating roles and often do in experimental work. Belief that hypnosis is a matter of a weak will dominated by a strong will is entirely a misconception. The best subjects are highly intelligent, normal people, the feeble-minded and the psychotic and many psychoneurotics are either difficult or impossible to hypnotize.

Since hypnosis depends primarily upon cooperation by the subject the *control of the trance* rests largely with the subject. No subject can be kept in a trance for an unreasonable length of time without his full cooperation and the removal of the hypnotist from the hypnotic situation by one means or another disrupts the interpersonal cooperation necessary for the continuance of the trance. Thus no subject can be left accidentally or intentionally in a trance for an indefinite period.

dent the illogic of assuming that the time- and situation-limited hypnotic trance can bring about significant harmful effects, when earnestly desired beneficial effects are so hard to achieve

### THE TECHNIQS OF HYPNOTIZING

The technic of inducing hypnosis, contrary to long-established traditional superstitious ideas of eye fixation, crystal balls, and passes of the hand, is primarily a function of the interpersonal relationships existing between the subject and the hypnotist

Hypnosis is not a mystical magical thing that follows a definite rule-of-the-thumb or a special abracadabra. Practically all normal people can be hypnotized, though not necessarily by the same person, and practically all people can learn to be hypnotists. Hence any technic that permits the hypnotist to secure adequate and ready cooperation in this highly specialized interpersonal relationship of hypnosis constitutes a good technic. The able hypnotist is the one who is able to adapt his technic to the personality needs of his subject. Thus, some subjects want to be dominated, others coaxed, still others to be persuaded. Some subjects want to dominate the situation and place the hypnotist in the role of an assistant who merely guides. Some prefer to be hypnotized by a wealth of repetitious suggestions, and there are those who like to resort to an introspective experiencing of the process of going into a trance. Sometimes the situation is one of authority-subservience, or it may be one of father-child, or again physician-patient, and often that merely of two equals intensely interested in an important problem.

Properly, the hypnotist should have a good appreciation of his own personality and capabilities so that he may adapt himself to the specific personality needs of his subject. In the majority of instances, especially in medical hypnosis, the physician-patient relationship is ideal and satisfies adequately the personality needs of the subject.

The actual procedure best employed when the problem is not controlled experimental work consists of giving the subject a preliminary explanation of what he may expect, thereby correcting any misapprehensions he may have. At the same time this suggests indirectly to him his course of behavior and response. This is followed by a series of suggestions to the effect that he will get tired and sleepy, that he will go to sleep, and will feel himself going to sleep, that he will notice increasing lassitude of the body and an increasing feeling of comfort and satisfaction as he continues to sleep until he falls into a deep, sound, restful sleep. Every effort should be made to make the subject feel comfortable, satisfied, and confident about his ability to go into a trance, and the hypnotist himself should maintain an attitude of unshaken and contagious confidence in his subject's ability. A simple,

earnest, unpretentious, confident manner is of paramount importance unless one wishes to be a vaudeville performer. Only then are histrionics warranted.

Once the hypnotic trance has been induced there is need to keep the subject in the trance until the necessary work has been completed. This is best done by instructing the subject to sleep continuously, to let nothing disturb him, to enjoy his trance state and above all to enjoy his feeling of comfort, satisfaction and full confidence in himself, his situation and his ability to meet adequately and well any problem or task that may be presented to him.

The awakening of the hypnotic subject is a simple procedure even with those subjects who wilfully insist upon remaining in the trance. Usually simple instruction to awaken is sufficient. If the subject resists, awakening simple persuasive suggestions will suffice.

Of great importance in inducing trance states and trance behavior is the allotment of sufficient time for the subject to make those neuro- and psychophysiological changes necessary for certain types of behavior. To rush or force a subject often defeats the purpose.

hypnotist wishes included in the trance situation, and it has the effect of dissociating the subject from all other things. This rapport the hypnotist may transfer by appropriate suggestions.

*Catalepsy* is a second phenomenon which illustrates clearly the tremendous psychosomatic significance of hypnosis. This is a peculiar state of muscle tonus which parallels *cerea flexibilitas* of the stuporous catatonic patient. The subject holds his arm up in the air, maintains any awkward position given him by the hypnotist, and shows a failure of normal fatigue reactions. Concomitant with it are a loss of the swallowing reflex, a dilatation of the pupils, a loss of facial mobility, and a definite slowing of all psychomotor activity. Yet, upon instructions by the hypnotist, the subject can perform adequately at a motor level equal to the waking capacity and often at a level that transcends it.

*Sensory changes*, or alterations in sensory behavior, of both a positive and a negative character are frequent and often undetected. Blindness and deafness to things not included in the hypnotic situation often develop to a degree that resists clinical tests. There also occur spontaneously anesthesia, analgesia, and other types of sensory disturbances. Additionally these sensory phenomena can be induced by appropriate suggestion. A detailed account of these types of psychosomatic manifestations is reported by the author in the January, 1943, issue of *Psychosomatic Medicine*. Their presence is often of great importance in therapy since they serve so well to make the subject appreciate his trance depth and to direct the hypnotist's attention to unexpected psychosomatic implications that need to be considered in the hypnotic procedure.

*Amnesia and other memory alterations* constitute another type of hypnotic phenomena of extreme interest to the medical man. Usually after a deep trance the subject has a more or less complete amnesia for all trance events. This amnesia can be controlled by the hypnotist through instruction to the subject, or the subject himself can deliberately set about recovering the amnestic material. In either instance, the forgotten memories may be recovered in full or in part according to the instructions given or in accordance with the subject's needs. This amnesia is of profound importance in psychotherapy since it permits the therapist to deal with painful memories without arousing the subject's waking resistance and defensive reactions.

In contradistinction to hypnotic amnesia is the capacity of the hypnotic subjects to develop *hyperamnesia*, that is, increased memory ability, and to recover memories of past experiences long forgotten and actually inaccessible in the waking state. Traumatic, painful, forgotten experiences and memories that often constitute a point of origin in serious personality disturbances are frequently readily accessible under hypnosis, can be easily recalled by the patient and a foundation laid in the trance state for their integration into the waking life of the



rial or to disclose necessary information otherwise inaccessible or which the personality is not yet strong enough to face. Or the subject may see vividly and clearly in a crystal the enactment of long forgotten traumatic experiences and thus achieve a realization of their actuality and reality to him as a person.

*Posthypnotic suggestion* is one of the most significant of all hypnotic phenomena. By this measure a subject can be given instructions in the trance to govern his future behavior, but only to a reasonable and acceptable degree. Thus, the subject may be instructed that at some future date he is to perform a certain act. At the specified time the subject executes his bidding, but believes his performance self-ordered and spontaneous. As a therapeutic measure, posthypnotic instructions are of great value, but if improperly used they are ineffectual and futile. They need to be used primarily as a measure of providing the patient with an opportunity to develop insight and to integrate his behavior.

*Somnambulism* is another form of hypnotic behavior always significant of a deep trance state. In this condition, the subject behaves and responds as if he were wide awake and may even deceive observers with his seeming wakefulness. This state is the most suitable for the deeper forms of psychotherapy and can be induced by repeated hypnosis in at least 70 per cent of all subjects.

### THE VALUES OF HYPNOSIS

To the medical man, the values of hypnosis in medical science are of first importance. That hypnosis can contribute to the scientific study of human behavior, normal and abnormal, is self-evident, since it permits experimentation and investigation not ordinarily feasible and under conditions difficult or even impossible to obtain in the waking state. Thus, it possesses values of a basic character in the development of a more adequate scientific understanding of the medical problems arising from disturbances in human behavior and adjustment. These values alone would warrant continued hypnotic work.

Additionally, hypnosis possesses other values of paramount interest to the physician as an individual. Foremost of these is the education it gives the medical man in understanding, sympathizing and dealing effectively with that vast array of emotional conflicts, fears, anxieties, uncertainties, psychoneurotic complaints and psychosomatic disturbances that constitute so large a part of the problems presented to every medical man. These are problems that cannot be treated with drugs or surgery nor with the simple statement that "there is nothing wrong with you physically."

Such patients are in need of therapy, therapy of the class that falls under the heading of the "art of medicine." This is essentially a physi-



cian patient relationship that permits the physician to enable his patient to capitalize upon every positive thing he has to reach a satisfactory adjustment in life rather than become psychologically invalidated.

The physician who learns hypnosis and thus learns how and when and why to give suggestions effectively to his hypnotic subjects is literally taking a postgraduate course in how to suggest to his patients the attitudes, insights, understandings and methods of behavior that will enable them to adjust more adequately in life. In the general practice of medicine it is not only the drug dispensed but the physician's manner of handling the patient that constitutes the actual turning point in the patient's illness: his attitude toward himself and toward life. The entire history of medical practice emphasizes the tremendous factor of the human relationship, and that physician who has trained himself in hypnosis has acquired special experience that stands him in good stead in building up his art of medicine even though he may not utilize hypnosis directly.

## ILLUSTRATIVE CASE HISTORY

To illustrate the actual application of hypnosis to a specific medical problem, the following case history is presented. This account has been selected because it demonstrates clearly both the medical and the psychological aspects of a total problem reflected in a single symptom which could easily have been the point of departure for a serious, prolonged neurotic disturbance, and also because the account permits the reader to recognize readily the psychological significance and the rationale of each step in the therapy employed. The total time spent in treating the patient was slightly over three hours. Such an expenditure of time was warranted by the nature of the case and justified by the results obtained, and it illustrates the need in hypnotic therapy to allot time as freely as is done in surgery.

That so systematic and elaborate a procedure of hypnotic therapy was necessary for the patient described is open to question. Perhaps a simpler approach would have succeeded, but adequate therapy of the patient was the goal sought, and there was no thought of experimentation to determine how economical of effort the therapist might be in handling this particular problem. Failure in attempts at hypnotic therapy always increases the difficulty of further efforts at therapy. Hence, for the benefit of the individual patient, extensive care and effort is always warranted.

The patient, a woman in her middle thirties, was referred to me by her physician for hypnotic therapy because of hysterical urinary retention of fourteen days' duration, and an increasing neurotic reaction of fright, terror and panic over her condition. The history secured contained the following significant facts:

She had been recently married after having despaired of marriage for many years because of her belief that she was not physically attractive. Following a brief honeymoon, she had developed an acute nonspecific urethritis and cystitis, which, because of her educational background in medical science, had frightened her seriously. The infection yielded rapidly to medication, but during the course of her treatment she had been catheterized several times. This had embarrassed and distressed her greatly. Just before her discharge from the hospital as recovered, her husband received notice to report for induction, a notification arriving much sooner than had been anticipated. She reacted to this with intense grief but soon composed herself and began to rearrange her plans for the future.

Some hours thereafter she had found herself unable to void. Repeated futile efforts over a period of several hours had increased her anxiety and discomfort seriously and she had to be catheterized.

Thereafter catheterization twice daily for two weeks was necessary, since various measures of encouragement, reassurance and sedation failed. The patient responded to this with increasing alarm and terror because of her helplessness. Nor was the general situation helped by the patient's own realization that her symptom might be hysterical, since she regarded hysteria as much worse than an organic disability.

The actual therapeutic procedure was simple. She was given an evening appointment so that ample time free from interruption would be available. The history furnished by her physician was confirmed and elaborated by a casual, comfortable questioning and discussion of the patient's problem as a means of alleviating her anxiety.

She was then sent to the lavatory with firm instruction to discover if her symptoms still persisted, and to make certain that she really needed treatment. Thus she was given the first real doubt about the continuance of her distress. To have sent her to the lavatory with instruction to void would have entailed therapeutic failure since inability to obey such a command would seemingly have demonstrated my incapacity to handle her problem. But to be sent to discover if she really needed treatment had the effect of convincing her of my complete confidence in my therapy and of my unwillingness to use it unless actually required. She returned to report that her symptom was still present whereupon she was asked if she wished me to proceed with therapy. Upon her assent, the explanation was offered that before therapy would be undertaken at all it would be necessary to discover how capable a hypnotic subject she was as a preliminary to dealing with her problem therapeutically. She expressed some disagreement at this delay in therapeutic hypnosis but recognized the desirability of permitting me to follow my own procedure.

Accordingly a light trance was induced and ampic hypnotic phenomena elicited and this was followed by the induction of a fairly deep trance during which the patient was called upon for a controlled manifestation of hypnotic phenomena. This procedure was simply a means of testing her before really that she could execute hypnotic instructions readily and accurately and commence a process of building up her confidence in her ability to obey any instructions given in her

her thinking constructively so that she would be able to face her problems adequately instead of retreating from them into neurotic illness. However, at no time was any direct psychological interpretation made of her urinary retention. In fact, it was not even mentioned specifically. Instead, reliance was placed upon the patient's own thinking and intelligence to make the proper psychological interpretation of her symptom when she became ready for that realization.

When the patient seemed to have adequate understanding of her situation and its probable significance to her personality, return was made indirectly to her symptom. In the guise of casual conversation, she was reminded of the practice of little children at play to suppress the need for urination until the last possible moment and then to rush frantically to the bathroom where any unexpected delay would result in a wetting of their clothes.

As soon as the patient understood this general statement, she was asked with much urgency to tell me approximately how long it would take her to reach her home after I dismissed her, what route she would follow, an approximation of the distance from the pavement to the front door, the location and the length of the stairway leading upstairs, and how far down the upstairs hallway the bathroom was located.

When the patient had given this information as accurately as she could, she was given a rapid series of urgent, strongly persuasive suggestions to the effect that

- 1 She would leave for home feeling generally comfortable and at ease and not thinking about anything specific but just simply absorbed in quietly enjoying the ride home,

- 2 That during the last twenty minutes of the trip home there would come to her mind vague fears that she might wet herself, which she would promptly suppress, only to have them recur with increasing frequency and insistency until finally they would become an annoying and even distressing conviction that if she did not arrive home soon she would surely wet herself,

- 3 That the last five minutes of the trip home she would spend in a state of feverish anxiety and that she would be unable to think of anything except whether she would be able to hold out long enough to rush through the door, up the stairway, and into the bathroom where she then could relax completely and be comfortable all over,

- 4 That when she was relaxed and was comfortable all over, she could then have a full recollection and understanding and memory of all those things she needed to know to meet her life situation without handicaps

These suggestions were given repetitiously, urgently and with great rapidity until it was certain the subject understood them sufficiently well to execute them. Then after instruction to have amnesia for all trance events and suggestions, she was awakened and promptly dismissed.

Her husband, who had accompanied her, was instructed to drive home quietly, commenting only on the beauty of the night, acceding to any demands of his wife that he drive faster but to keep within the speed limits, and asking no questions of any sort.

Subsequent reports from the husband, the patient and the referring physician disclosed the effectiveness of these suggestions and the suc-

cess of the therapy both in relation to her symptom and her adjustment to her husband's military status. Inquiry a year later disclosed no recurrence of her problem.

#### CONCLUSION

To summarize, the age-old attitude of superstitious awe, fear, incredulity, and antagonism toward hypnosis is now being rapidly replaced by an appreciation of its scientific values. In its place is a growing constructive recognition of hypnosis as both a therapeutic medical procedure and a means of acquiring a sympathetic understanding and appreciation of human nature and behavior requisite to the adequate practice of psychotherapy and the art of medicine.

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## SUSCEPTIBILITY TO ACCIDENTS

FLANDERS DUNBAR M.D., Ph.D., M.D.Sc.D

SOME physicians may be surprised to find a discussion of susceptibility to accidents in a symposium on psychosomatic medicine. But the accident habit or accident proneness is a syndrome in dealing with which the psychosomatic approach is essential even though the mechanisms involved, physiological as well as psychological, are of a different nature from those encountered in syndromes such as hypertension or peptic ulcer where the vegetative system plays a relatively greater role.

The psychosomatic approach means thinking in terms of the necessity for the organism to maintain a homeostatic equilibrium within itself and within its environmental field. Hence in the science and practice of medicine there is need for a new approach to etiology based on psychosomatic concepts. Here the major contributions have come from physiologists on the one hand and from medical psychologists on the other. It has been difficult, however, to bridge the chasm between these two disciplines.

campaign for improving safety devices and has as well developed an educational program on the basis of an analysis of the kind of unsafe acts which result in accidents. Yet in the estimate given in the last report, over a period of thirty years only a saving of some 275,000 lives is claimed, or less than 1 per cent of the total of the deaths each year from accidents.

It has been calculated that there were 460 million man-days lost in 1941 due to all kinds of accidents, or the equivalent of the work of 1,500,000 persons.<sup>1</sup> Injuries account for four times as many lost man-hours as do strikes with 50,000 manufacturing workers absent every day because of accidents.\* The Office of War Information<sup>2</sup> states that the plants which have been most successful in reducing accident frequency are those in which management and labor, using government-industry facilities, have pooled their resources to operate against both the physical and the psychological factors that cause accidents.

Those interested in decreasing the accident rate among workers are beginning to realize that improvement in safety devices in industrial plants is inadequate on two counts: (1) more than one half of the 4,000,000 workers killed or injured each year are killed or injured outside the plant, and (2) the majority of accidents are caused by the man and not by the machine. The consensus of reports made during the last ten years by insurance companies, the National Research Council and the Industrial Health Research Board of Great Britain is that from 80 to 90 per cent of all accidents are not due to defective machinery, to a physical or mental defect, or to lack of skill in the worker, but to an *x factor* in the person injured. The fact that three such widely different and unrelated groups have reached the same percentage range suggests that there must be some factual foundation for such a conclusion. Hence the nature of this *x factor* becomes a matter of major concern.<sup>3</sup>

#### ATTEMPTS HAVE BEEN MADE TO DETERMINE THE X FACTOR IN ACCIDENT-PRONENESS

About twelve years ago when the National Research Council<sup>4</sup> began to investigate accident-proneness in commercial drivers of four large utility companies, no way was found to distinguish the driver with the high accident rate by psychological or personality tests. But a shift of 5 per cent of the personnel with the highest accident records to other jobs reduced the accident rate by 80 per cent, or to one fifth of the original rate. It was even more significant that these 5 per cent of employees who were shifted to different jobs continued their high

\* It is reported by the Office of War Information that deaths and injuries on the job in war plants are causing the loss of 270 million man-days a year, or the equivalent of the withdrawal of 900,000 workers for a full year from the production lines.



accident record no longer through driving cars but for example, through slipping falling or shutting doors on fingers. Accident proneness has been observed even in animals. Gantt in his study on neurotic behavior in dogs reported the accident habit in a dog which he studied for a period of ten years.

The 1943 edition of *Accident Facts* reports that while the number of traffic accidents was cut down during the year 1942 the figure was not reduced in proportion to the reduction in driving miles. During the same period household accidents increased. The total cost of accidents in 1941 was about \$4 000 000 000 but in 1942 it was \$6 200 000 000. All this shows (and much more evidence could be adduced) that there are accident prone persons among us and that they constitute a health risk to themselves and to other people moreover that the risk cannot be dealt with adequately merely through education of accident prone persons or by improvement of the machines used.

may have resulted from factors completely beyond their control. Hence there is immediate need for a basis of distinguishing the accident-prone more accurately than is possible in terms of the accident history.

During the last fourteen years, in connection with a study of serial admissions of patients with cardiovascular disease to a general hospital, some clues were obtained, almost fortuitously, relative to the kind of person who is likely to be accident-prone or to develop the accident habit. Because cardiovascular disease outranks all other illnesses as occasioning mortality and disability, and because medical understanding of its causes is inadequate, it was decided to study the personality as well as the clinical course of all patients between the ages of fifteen and fifty-five years admitted to the hospital. Since the scientific investigator likes to have a control group, the patients on the fracture ward were selected for comparison as probably being more representative of the healthy population than any other group in the hospital, inasmuch as "accidents happen by accident." As the study progressed it became evident that these patients had too many personality traits in common to be considered a control group although their personality profiles proved an enlightening contrast to the personality profiles of persons suffering from other syndromes.<sup>6</sup>

One significant trend in current comments on the problem of major chronic psychosomatic disorders is toward the realization that in this field one label quite frequently covers several distinguishable syndromes. Diabetes, hypertension and rheumatic fever used to be considered single disease entities. Now we speak of different types of diabetes, different types of hypertension and different forms of rheumatic disease. Likewise, in the study of accident patients a single personality type stood out as characteristic and the first comments published on the personality of the accident-prone were largely colored by observation of this one clear-cut type. A number of persons originally considered as atypical were subsequently discovered to belong to one of two clearly distinguishable sub-types of the accident-prone personality.

The highest accident record and fortunately the most easily diagnosed occurs in the Type B personality group, comprised mostly of males. This is the type that colored the original profile of the accident-prone. Type A, comprised mostly of females, is more difficult to diagnose and has a lower accident record, except for the males in this group whose record is very high. Type C, a somewhat smaller group, which includes a relatively small percentage of women, is the least clearly defined. In order to indicate the differences among the three types, and also to show how clearly the three as a group may be distinguished from the profile for another syndrome, the profile for patients with coronary insufficiency is here reproduced in a parallel column with that for patients with fracture.



INDIVIDUAL PICTURE (*Continued*)

## Fracture

d *Social Relationships* "Good fellow" No marked tendency to dominate or submit. Tendency to aggressive self-reliance. Not likely to curry favor with either sex. Tendency to eccentricity in Type B

e *Sexual Adjustment* Superficially good. No tendency to emphasize sexual problems, combined (especially in Type B) with lack of real emotional contact. Careful to avoid infection in promiscuous relations but without exaggerated fear

f *Attitude toward Family* Dispersion of tendencies among Groups A, B, C. Trend toward irresponsibility in Group B

6 *Characteristic Behavior Patterns* Make up their minds definitely and quickly. Focus on immediate values rather than long-range goals. Social rather than power interest. Striving toward integration and autonomy, outside of authoritarian hierarchy. Tendency to attach emotions to people and immediate concrete experience. Little emotional interest in intellectual values and verbalization. Defensive tendency to appear casual about feelings and personal problems. Group B show marked adventurous trend and avoidance of responsibility. Living from day to day

7 *Neurotic Traits* High percentage of early neurotic traits, especially lying, stealing and truancy, sleep-walking and sleep-talking. Later life almost no obvious neurotic traits (some infantile trends) except for small group, particularly women, with phobias, especially fear of falling

8 *Addictions and Interests* Tendency to use stimulants (coffee, cigarettes, alcohol) for pleasure or to let off steam. Marked interest in competitive sports or gambling (football, baseball, racing, auto-racing), and machinery. Practicing orthodox authoritative religion (institutionalized super-ego)

## Coronary Insufficiency

d *Social Relationships* Generally respected. Tendency to dominate. Argumentative with men, attentive to women

e *Sexual Adjustment* Role of exemplary husband (and father) combined with frustration and often secret promiscuity, high venereal disease rate. Emphasize sexual problems (overt anxiety)

f *Attitude toward Family* Hostile toward father, passive though often hostile and fearful toward mother. With wife and children attempt to be boss and "carry the burden," combined with demand for care and attention

6 *Characteristic Behavior Pattern* Compulsively consistent action. Tendency to work long hours and not take vacations. Tendency to seize authority, dislike of sharing responsibility. Conversation an instrument of domination and aggression. Tendency to attach emotions to ideas and goals. Articulate about feelings. Living for future.

7 *Neurotic Traits* Few early neurotic traits, tendency to brood and keep their troubles to themselves. In later life inner tension and a tendency to depression which is rarely admitted to others, together with compulsive asceticism and drive to work.

8 *Addictions and Interests* Tendency to take stimulants to help keep on working (overwork). Little interest in sports, few hobbies. Skepticism about religion. Marked interest in philosophy

## INDIVIDUAL PICTURES (Continued)

## Fracture

9 *Life Situation Immediately Prior to Onset* Situations threatening individual autonomy in which direct release of aggression would be too costly. Often connected with actual or contemplated shifts in job.

10 *Reaction to Illness* Bravado or fatalism about specific symptoms or else exaggerated interest (insecurity) plus poor tolerance of pain, either one frequently combined with tendency to exploit injury for compensations, financial or other.

11 *Area of Focal Conflict and Characteristic Reaction* Authority avoidance. Attempt to establish personal autonomy to avoid authority relationships (marked passive-active conflict). Little identification with authority figures or concepts.

## Corrosary Inefficiency

9 *Life Situation Immediately Prior to Onset* Exposure to shock-experiences in job or in relinquishment of authority.

10 *Reaction to Illness* Tendency to minimize symptoms, and self-protect.

11 *Area of Focal Conflict and Characteristic Reaction* Attention to work, authority, identification with authority and authority concepts.

Though Nick showed no evidence of being cooperative and was not as friendly with his master and others as most dogs, nevertheless he still appeared to learn rapidly. For example, although he would not come into the automobile when called to do so, he would immediately rush to the car whenever anyone got in or blew the horn in preparation to leave.

It is interesting that Nick showed this tendency during 1943 as well as previously. In 1937 he frequently got tangled in his chain, binding and hurting himself. In 1943 on the farm, he twice fell into an abandoned privy from which he could not extricate himself and where he remained for some hours until he was located by his barking. He would frequently knock into things, get under people's feet, run into machinery, etc. On one occasion at night he followed my car without my knowledge, but as he could not overtake me, I met him on my return homeward. After passing him going in the opposite direction, I turned around and went back, but he again had recognized my car and was again running toward me. I put on the brakes, but he continued running into the car which knocked him down and dragged him along, resulting in two scalp wounds. However, he trotted on home at a rapid pace, so that I did not find him until I had also arrived.

The accident-prone personality Type A is more constricted than Type B, and the life history is marked by periodic attempts to assume responsibility, although with the same striving for independence and autonomy outside the sphere of authority relationship. These attempts nevertheless break down when the individual autonomy is threatened by an unavoidable conflict with authority. When such conflicts arise Type A may shift to the Type B pattern of changing job or family relationship or he may have an accident, or he may experience both. Hypertension is more likely to occur in this personality type than in Type B or C, as those who are familiar with the hypertensive personality would surmise.

#### SUMMARY RELATIVE TO PSYCHODYNAMICS

Any dynamic formulation relative to the profile of these accident-prone personalities should begin with an investigation of the nature of their defenses. By focusing their values on immediate concrete experience, striving to find satisfactions and security outside the authoritarian hierarchy, and avoiding any marked submission or domination in vocational or social roles, accident-prone persons get along without serious conflicts with authority. The defenses work most of the time. When thwarted, deprived, or subjected to unusual strain such as unemployment, or the pressure of a mother-in-law in the family, these persons "do something" to modify the situation or get away from it instead of keeping their anger bottled up inside. It is significant that these patients have a health record far above the average.

When the characteristic defenses fail and conflict with authority becomes unavoidable, the accident happens. Aggressiveness may break out in an act which appears to punish the victim or those responsible.

for his frustration or both. Or it may come near enough to the surface to cause the kind of confusion which leaves the person defenseless in the danger situations normally encountered from day to day. Unlike depressed persons who consciously attempt suicide the accident prone individual usually reports no conscious premeditation. It is interesting, however, that he occasionally reports a dream or a "hunch" that "something was going to happen today" or that he "was going to have bad luck." This trend is illustrated by the statement made so frequently by these patients after the accident has happened: "you can't get around fate. I got mine today, you'll get yours tomorrow." (For illustrative histories see Dunbar<sup>6</sup>)

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## TRAUMATIC NEUROSES

JOHN J. MOONIFAN M.D., D.Sc., F.A.C.S.\*

### NOMENCLATURE ETIOLOGY

THE so-called "functional disturbances of the nervous system" are frequently encountered in association with trauma, and less often with nontraumatic and even with medical conditions. The prefix 'traumatic' is hence regarded by many as a misnomer because the essential symptoms appear without trauma for example as the outcome of worry, fear and strain from a great variety of nerve stressing causes. The conjoined name has existed so long however that attempts to rephrase it have thus far been unsuccessful and thus it is still in general use. Personally I cling to the accepted nomenclature although well aware that the ultramoderns in neurology and especially in psychiatry would abandon the title and rebaptize the rebellious offspring and confirm it and perhaps even reform it by adopting a more lurid scientific cognomen.

purposeful, but is the outgrowth of injudicious remarks made in the presence of the patient or later repeated to the latter by others. A certain class of physicians is fond of dilating on the subject of "possible internal injuries," "brain damage," and "spinal trouble" in the presence of an injury respectively to the abdomen, head or back. The statement "you may be a cripple for life" sufficiently often repeated is certainly not likely to increase optimism or act as a stimulus toward recovery. If this is true where there is no special object to be attained by prolonging disability, it is increasingly true when there is gain in view.

In years gone by, railroad accidents were supposed to inflict special forms of neural injury, and to these the name "spinal concussion," "railroad spine," and "railroad brain" were given. Erichsen, about 1874, thus christened this ailment and since then it has been occasionally heard of, but only in connection with claims for damages.

Strangely enough, of the fifty-three reported cases in Erichsen's two books, less than one third of the patients were hurt in railroad accidents, and, as stated long ago by the late Pearce Bailey, in the total number of cases reported there is not one in which a diagnosis of "spinal concussion" due to "molecular changes" would stand present-day analysis. The only case of the group that was subjected to autopsy was clearly one of locomotor ataxia, and with our present knowledge it certainly would not be denominated either as "railroad spine" or "spinal concussion." Several of the cases cited by Erichsen were very severe traumas of the spine that today would be recognized as fractures of the laminae or other vertebral processes, others less severe were intraspinal hemorrhages.

Oppenheim is responsible for the name "traumatic neurosis." Various neuroses are denominated by other prefixes, seeking to indicate thereby the causative factor, for example, "anxiety neurosis," "fatigue neurosis," "fear neurosis," "fright neurosis," "gastric neurosis," "endocrine neurosis," "pelvic neurosis," and many others. In addition the term "complex" is added to many cases in which the element of fear, anxiety, worry, expectancy, desire or other factor appears.

The condition has been still further clarified by insurance statistics, and it is from reliable clinical and statistical sources that the best knowledge is obtainable.

A great many extreme views have been entertained and expressed respecting these subjective nervous disturbances, one group of observers maintaining that the symptoms are assumed and purposeful, and, in reality, nonexistent, another group maintaining their reality, severity and permanency.

#### CLASSIFICATION

These posttraumatic *functional* disturbances of the nervous system were formerly rather sharply divided into the two classifications of

neurasthenia and hysteria. However, this differentiation is now apparently less definite than heretofore.

*Neurasthenia* was broadly defined as a general state of nervous incapacity characterized by inability to maintain sustained nervous and physical energy. The causation and symptomatology were very diverse but muscular weakness and vascular hypotonicity were prominent features.

*Hysteria* was regarded as a condition characterized by underlying stigmata which manifested themselves chiefly by alteration in the motor-sensory mechanism. These resulted in disturbances of motor activity (such as convulsions and paralyzes) or sensation (such as areas of superficial or deep anesthesia). It was and is known as the great imitator because it could feign almost any physical or mental condition to which flesh was heir. An arm or leg, for example, was apparently incapable of motion, and superficial sensation was lacking therein. But despite these obvious defects, there was no actual structural defect. Phantom tumors or even pseudo pregnancy were noted. Trances, alterations in personality and curious bizarre effects of all parts of the body were in evidence.

*Neurasthenia's* background was instability of the nervous system, congenital or acquired.

3 They are frequently the outcome of, or motivated by, suggestion, fear, anxiety, desire, revenge, escape, frustration, financial gain or reward

4 They are very rarely seen in patients who are injured under ordinary circumstances, but are very common within the medicolegal framework

5 They develop very often from unwise suggestions or actions made by doctors, nurses, physiotherapists, lawyers or others

6 Recovery usually occurs after the motive has been satisfied, this result is frequently very prompt after a legal settlement is obtained

7 They may occur from many traumatic or nontraumatic sources, and the manifestations are quite similar irrespective of the originating cause

8 They occur in wartime or peacetime, and the sources, though vastly different, produce nearly identical symptoms In war-injuries as in civil injuries, the badly hurt patient rarely develops a traumatic neurosis

9 They may develop from the sights or sounds of a traumatic incident irrespective of any physical contact

10 They are prolonged and often become definite complexes if legal machinery postpones a settlement after surgical cure is complete or has reached a stationary period

11 They are fostered by frequent changes of medical advisers, especially when the financial weekly award is enough to provide ordinary comforts during idleness

12 They are rich in subjective and poor in objective evidences, and most of the assertions are entirely disproportionate to the actual injury

13 They have a posttraumatic set of symptoms in legal cases quite different from those characteristic of identical injuries when there is no financial end in view

14 They are loud in assertions but meager in confirmatory proof, and the findings in many cases are indicative of long-standing nervous instability rather than recently acquired symptomatology

15 They occur in both sexes, in all walks of life, but are apparently more frequent in the Jewish and Latin races Neurasthenia is more common in men, and hysteria in women

In World War I, the designations *shell shock* and *psychoneurosis* were used in the early stages of the conflict, but later the term *neurocirculatory asthenia* was substituted, and that and *psychoneurosis* are the titles now employed in World War II The causation and symptoms are substantially the same in both wars, as indeed they have been ever since the days when Erichsen coined the term "railroad spine" It is to be remembered that the condition may occur from many non-traumatic sources, and the symptomatology is practically the same whatever the real or asserted origin if properly motivated

There has been admittedly a definite increase in the neurotic population not only as to the functional but also as to the organic manifestations. *Schizophrenia* (dementia praecox) of many varieties has become exceedingly common and is now probably the leading source for custodial care. This disease has become a problem in industry because it often appears in an efficient employee who has hitherto been apparently perfectly well. In most of the cases I have knowledge of the patients blame their plight on home troubles, financial difficulties, alcohol, insomnia or sexual conflicts. The family and personal history practically always indicate neural instability. Trauma in my experience is not a factor inasmuch as I have never had a posttraumatic case, even in head injuries.

After recovery from the attack, the problem of returning these men to their former jobs becomes important. In my own railroad practice it has been the medical department's custom to select and retain employees if the existing physical ailment is not a menace to (1) the employee himself, (2) the public and fellow employees, or (3) property. Further in the New York City Transit System we classify employees into four groups:

1. Physically fitted for any duty
2. Physically fitted for selected duty
3. Physically fitted for minor duty
4. Physically unfitted for any duty

by some to be traumatic in origin, but that opinion is no longer tenable. Much of this etiologic confusion reverts to the days long ago when such factors as alcohol, syphilis, gout and trauma were assertedly the culpable quartet in a wide variety of human ills. The first three of these criminals are now relegated to their proper place, but the "and trauma" persists. Aside from actual origination of the neuroses, trauma is accused of activating or accelerating the condition in those who are concededly predisposed or apparently cured or in a quiescent period. This assertion is naturally open to serious question in the majority of instances inasmuch as the neuroses are independently subject to periods of accession and remission as incidents of their normal life history. It is also asserted that many persons are born with or acquire neural instability, and only await some "spark to inflame" their susceptible framework. Likewise it is alleged that trauma or some other incident "lowers the resistance" and thus a neurosis occurs. Any such reasoning as this is usually remote or speculative, and often is an attempt to fit into an *effect* a possible or improbable *cause*. The "spark" and the "lowered resistance" theories would account for almost unlimited manifestations, and if carried to the extreme could be regarded as universal etiologic backgrounds for any type of illness. Clinically we do not subscribe to any such relationship in ordinary disease processes, and there is basically no sound reasoning to consign the neuroses into any like category.

#### A NEW VOCABULARY FOR OLD PROCESSES

My own increasing experience with the injured leads me to practically the same conclusions as at the time of my original publications. As indicated, the nomenclature has changed, just as it did in all the period since the neuroses were first described. Many attempts have been made to rechristen this neurologic problem child, but no definite name as yet has been agreed upon. "Railroad spine" was succeeded by "traumatic neurasthenia," "psychasthenia," "traumasthenia," "shell shock," "neurocirculatory asthenia," "phrenasthenia" and other names. Today we hear of such appellations as "anxiety neurosis," "fear neurosis," "litigation neurosis," and many more.

Kubie<sup>2</sup> well states "It is not strange that in the effort to characterize widely different psychosomatic relationships, a host of terms has come into use, such as conversion symptoms, hysteria, body reference, body representation, somatic compliance, organ inferiority, constitutional inadequacy, pathoneurosis, organ neurosis, actual neurosis, neurasthenia, sexual neurasthenia, hypochondriasis, hypochondriac, chronic invalidism. These terms have no constant usage. Their meanings overlap, their implications vary, and they fail to characterize the nature of the psychosomatic interrelationships which it is their purpose to indicate. It is this situation which has instigated the present

effort to bring some systematic order into this chaos, by arranging the phenomena in groups which have logical physiological and psychological implications." These psychosomatic processes (somatization) represent "any process by which tensions which are generated on the level of psychological experience are given some form of bodily representation and a partial discharge through anatomical and physiological disturbances.

#### EXPERIENCE WITH MILITARY PERSONNEL

Despite this newer vocabulary, the ailment still presents certain cardinal features that remain unchanged. One of the newest terms I have heard is 'psychogenic rheumatism,' a title bestowed by two Army doctors<sup>3</sup> who describe a series of military cases under their observation in a California hospital. In these joint pains and back ailments predominated, plus the dominant desire to escape from allotted duty, and in all of them the most searching examination failed to disclose any adequate basis for the many subjective complaints. When the wishful thinking of this soldier group was satisfied, usually a furlough or army discharge prompt recovery ensued. This is very reminiscent of what has been termed 'compensationitis' in civil life. During the Pearl Harbor attack I was told that our chief Army hospital had a large group of patients denominated by the military surgeons as Hawaiian 'mainland fever' cases. Most of them had vague pains in various joints and in the back, and also were weary because of alleged flat feet. When the attack occurred they promptly left the hospital en masse and returned to duty.

The great majority of these returning employees had previously been gainfully employed with good service records in various branches of the railroad service

The majority of complaints were of vague pains, frequently in the back, headache, dizziness and inability for sustained effort. In some cases there had been a definite accident incidental to training, and in one case a suspected vertebral disc injury had been operated upon twice with a resultant peroneal palsy

In most instances the men were returned to their former jobs, but the majority of them will be subjected to a medical check-up at frequent intervals and their service record will be closely supervised by the Medical Department.

It is said that one fourth of all those discharged from the Army and Navy at the present time are on a psychoneurotic basis, and in many instances the respective medical departments of the Army and Navy are of the opinion that an unwise selection was made by draft boards and others and that many of those who subsequently developed a neurosis were physically and psychically unfitted for military life. It is very unfortunate that this large proportion exists and I am not at all certain that branding a discharged soldier or sailor as a "psychoneurotic" may not have a lasting effect and become the excuse later on for a series of subjective symptoms which may more or less justly be said to arise from some accident occurring during civil employment.

The extreme care and attention given to injured Army and Navy men not in the combat zone unquestionably has a variable effect and as has been noted by practically all observers, the less the injury the greater the neurotic manifestation.

During my own experience in World War I, with a service of nineteen months abroad in the evacuation hospital center, I encountered very few neurotic cases, except those in the group which we labeled "S I W," meaning self-inflicted wounds.

During the Pearl Harbor attack I saw only one case in which a neurotic element occurred, and that was in the case of an aviator who had a minor scalp wound, associated with transient blindness. His condition was promptly recognized and no special attention was given him and he recovered spontaneously after a short time.

It is again pertinent to say that if there is a reward or a gain in view, that then we can be reasonably sure of a continuation of symptoms.

Once more, let it be stated that the nomenclature has been changed and the psychiatric flare or flavor has been added, but, nevertheless, the manifestations are essentially unchanged throughout the years. However, the extreme manifestations of hysteria are very rarely seen and indeed in recent years traumatic hysteria has been less frequent in my cases than hitherto. The dramatic hysterical convulsions which were sometimes erroneously called hysterioepilepsy are extraordinarily



rare now, whereas "fit-throwing" as an exhibit in court was formerly quite common. The hysterical manifestations that I now see comprise chiefly areas of alleged insensitivity and such claimed motor inability as lack of power to use an arm or a leg.

#### THE MODERN VIEW

The preceding paragraphs were written as the outcome of considerable reading and much discussion with neurologists, and at the outset, I believed that anything I wrote twenty or thirty years ago was completely outmoded. As a matter of fact, however, except for the nomenclature and minor additions and corrections, the situation clinically is practically unchanged.

Greater experience and wider and more exact knowledge are delimiting the role of trauma as a causative factor in many neurologic conditions and in well informed circles the diagnosis of "traumatic insanity," "traumatic brain tumor," "traumatic encephalitis," "traumatic choreo-phrenia" and many others is given very little credence. It was not so long ago that "traumatic paresis" from head injury was supposed to be quite rampant, but instead of trauma the spinal chord lesion has been substituted. As a matter of fact "traumatic tuberculosis" was also said to exist and likewise "traumatic appendicitis" and "traumatic pyloric ulcer." The fact remains that if there is any real etiologic traumatic relationship, clinical observation would be universally proclaimed rather than almost universally disclaimed.

Three fourths of this group recovered within two years of onset and a little less than one half in the first year of onset. The more the expected premium the less likely the cure.

Mention is made of the significant factor that in Denmark 93.6 per cent recovered owing to a lump sum adjustment, by contrast with Germany where only 9.3 per cent recovered on the installment plan.

Foster Kennedy, of New York, emphasizes<sup>4</sup> the fact that "Almost no body of men so easily falls a victim to *post hoc, propter hoc* reasoning as ourselves and especially perhaps in the matter of relationship of injury to disease." He notes that in World War I, millions of men were exposed to all kinds of stress and strain and structural injury and yet the incidence of nervous disease was not increased. He states, "The total incidence of insanity in cases of gunshot wounds of the head, according to British official records, is the same as that for the general male population, which varies from 0.34 to 0.35 per cent." He states that the same conclusion can be reached in regard to schizophrenia. Speaking, also, of multiple sclerosis, the parkinsonian complex, muscular atrophy, syringomyelia and brain tumor, all of these showed no increase as the outcome of war experience and indeed general paresis, at least in Germany, decreased.

As to the role of injury in epilepsy, Kennedy quotes British sources as saying that up to the end of the year 1920 the Ministry of Pensions had recorded 18,000 cases of gunshot wounds of the head, in which 4.5 per cent of the patients were subject to epileptic fits. From French sources he states that the statistics show that the vast majority of cases of traumatic epilepsy are those in which there have been penetrating wounds of the head. In these the incidence of traumatic epilepsy is as high as 18 per cent. In all the rest, the incidence is only 2 per cent, and the incidence in the whole series of 377 cases is just under 10 per cent.

#### NEURASTHENIA, PSYCHASTHENIA, ANXIETY NEUROSES

Literally, neurasthenia means "weak nerves," the terms "nervous prostration" and "nervous breakdown" are synonymous, and since Beard's first description, it has been known as the "American disease." My personal belief is that "traumatic neurasthenia" will pass out of medical literature after the manner of "spinal concussion."

As a matter of fact, a diagnosis of neurasthenia is now rarely made by competent physicians or surgeons, and is still more rarely made by experienced neurologists.

The psychiatrists are adding their quota of names, and attempting an explanation of the many diverse symptoms on the basis of "escape from reality," "frustration," "evasion," "unfulfillment." Some of these hidden, determining or activating manifestations are brought out by psychoanalysis, seances or hypnotism.

**Definition**—Neurasthenia is said to be a functional disease of the nervous system due to a large number of causes, characterized by mental and physical incapacity for sustained effort, and presenting numerous subjective and some objective symptoms, particularly connected with the cardiovascular and muscular systems.

**Causes**—As stated these are very numerous and of them may be mentioned any of the factors of modern stress and strain that go to make up the strenuous life. Overwork, worry, grief, insomnia, alcoholism, exhaustion, moral, mental, social and physical excesses or indeed any set of causes that produce physical or nervous depletion may be a factor.

An unstable nervous equilibrium, hereditary or acquired, is usually a prerequisite and it has been truly said that the neurasthenic is born and not made, so strong is this element of predisposition.

A considerable number are due to disturbances of the physiology of the abdominal, sexual, thoracic and cranial organs, constituting the so-called reflex sources. Visceral crises, notably nephroposes and enteroptosis, produce or are associated with a certain proportion of cases. Another factor is acute or long-continued disease, or sudden changes incident to occupation, environment or situation in life. Disturbance of the internal glandular mechanism, notably of the thyroid and sex glands, is also an element.

and pelvic injuries are no more competent producing causes than injuries elsewhere inflicted

**Symptoms**—These are most readily grouped according to their regional distribution, and may be referred to as *cerebrospinal*, *motor*, and *visceral*, all of which are subjective mainly, but also objective. It is rare to have one group sharply defined, and the usual combination is the cerebrospinal

The *time of onset* varies, but it is usually prompt and rarely delayed more than a few weeks

**CEREBROSPINAL FORM**—Pains and aches in various regions are mainly complained of, and most of these cases start with the suggestion implanted by an injury to the head or back

"Cerebral neurasthenia" and "spinal neurasthenia" are sometimes used as denominative terms

*Headache* is one of the common symptoms, and this is usually referred to the region of the forehead or base of the skull, and is described as sharp and occasional or dull and constant. Usually excitement or sustained effort increases it

*Backache*, sometimes called "spinal tenderness," is the second most frequent symptom, and because of it the patient often infers "spinal trouble" and correspondingly worries respecting it.

This locational manifestation was the chief feature of the cases formerly diagnosed as "spinal irritation," "spinal concussion" and "railway spine"

The pain is ordinarily located at one or all of three locations, viz. Over the back of the neck about on a level with the vertebra prominens, about the midscapular level, and near the dorsolumbar junction. The pain is said to be accentuated by motion and pressure and the patient is sometimes able to delimit sharply the site by pressure of his own finger. Usually the pain is said to be superficial and over the spinous processes exactly in the midline, and less often just external thereto. If the pain occupies a wide area, it is almost invariably said to be located in the lumbar region. Pressure of the examiner's finger causes the patient to wince or exclaim, and occasionally a muscular contraction can be seen or felt. If these painful spots are marked by pencil or pen, the patient can accurately relocate them in genuine cases, this may be termed the "relocation test" and is applicable to any area of alleged tenderness.

The attitude of a patient with a tender back is often quite suggestive, as a posture and gait are assumed to relieve pressure and strain.

Occasionally the pain is said to be of a darting type, radiating toward the intercostal spaces or up and down the back or into the limbs.

*Aching in the limbs* is sometimes asserted, especially along the calf, and this gets worse from walking and standing, and hence the patient complains of weakness and incapacity for sustained effort and

pleids ready fatigability. The muscles thus become flabby and soft from disuse but actual atrophy practically never occurs except from disuse. Joint pain is occasional also and rheumatism and other articular ailments must be differentiated.

*Memory deficiency* may be complained of and the patient asserts that recent events especially are not sharply impressed less often memory for distant happenings is blurred. This memory trouble is also an evidence of tire or weakness and an added sign of the prevailing instability or incapacity for effort, and it by no means denotes any true mental failure or disease. All the detail of the accident however and the minutest circumstance intervening can usually be narrated with such effect that the patience of the listener will be taxed. Verbal display of this sort is common but it is much more frequent in non traumatic forms.

*Concentration loss* is allied to the preceding and is often the actual deficiency that leads to the suspicion that memory is hampered. Lack of attention and inability to "put the mind on it" are the main elements.

*Special senses* also sometimes manifest similar evidences of fatigue. Examination discloses no organic defects

*Vision* may thus be said to be diminished, this being a combination of lack of concentration and weakness of the muscles of accommodation. The patient may say that continued reading is impossible and in some cases the aid of glasses will be required. A host of visual subjective symptoms may be alleged, such as bright lights, floating specks, and other phenomena. Sometimes the pupil is quite large, but it is never irresponsive.

*Hearing* may be alleged to be deficient and auditory sensations of variable kinds may be mentioned, notably roaring and buzzing sounds, perhaps associated with dizziness or vertigo. Usually auditory symptoms are unilateral. These patients do not hear because they do not listen.

*Smell and taste* may uncommonly also be subjectively upset, but far less often than in hysteria.

**MOTOR FORM**—Here the injury is often to a well muscled part, as an arm or leg.

*Weakness of muscle* is a main feature, and the part is toneless, flabby and soft, but true atrophy does not occur, any shrinkage being due to disuse. Sustained effort of the part involved is lessened, and this may at times be measured by an instrument known as the *dynamometer*, a form of gripping machine designed to test the grip. This is so much under the control of the patient that it is practically a subjective test and of no more positive value than the response obtained by asking the patient to squeeze the examiner's hands. An improvised test of a similar form has occasionally been of some use, and all that is needed is an ordinary stationer's rubber band, the patient being requested to pull this against the resistance of his own hands or those of the examiner.

Early fatigue may prevent walking, standing, and working, and these people are given to sitting or lying around, thus increasing their muscular flabbiness.

*Tremor* is quite common and generally is increased by exertion, excitement, or emotion. It is most typically seen in the hands and fingers, and when not fully visible can often be made palpable by asking the patient to put the tips of four extended fingers against the examiner's palm, when a vibration will be readily apparent. Another test for this tremor is to ask the patient to support a thin sheet of cardboard or a blotter on four extended fingers. The type of tremor is usually fine ordinarily inconstant and irregular, and not of wide excursion. It may be seen in the tongue also, and is very often seen in the eyelids, especially when the patient is asked to stand erect with the eyes shut. The various muscles about the face less often tremble or twitch, notably those about the forehead, corners of the mouth, and chin. The

muscles of the trunk, back and limbs are occasionally the seat of tremors and these become more prominent during manipulation of the parts, the movement not infrequently then becoming very marked and almost convulsive or spasmodic.

*Reflexes* are usually exaggerated, notably those of the knee, elbow and wrist. A rather characteristic feature is the variability of the tendon jerks as on one occasion they may be quite lively and at another relatively normal and they may differ on opposite sides. The extent of reflex response is often a personal equation and may have wide variations and still be within the normal for that particular individual but persistently sluggish or absent reflexes, especially if bilateral and constant, should put the examiner on guard as to the possibility of some organic ailment. The superficial reflexes are less constantly affected than the deep but when involved show the same degree of varying exaggeration. After repeated tests of the reflexes the arm may act less promptly than at first thus indicating fatigue.

*VISCERAL FORMS*.—These are usually associated with that class of accident in which the patient is impressed with the idea of 'internal injury.'

frequently Actual urinary changes are rare, very occasionally transient albuminuria and glycosuria may occur, probably entirely dietetic in origin Indican is generally increased, but there is no basis for the belief once entertained that this ingredient in excess is typical of neurasthenics

*Sexual organs* are frequently less active, and at one time this condition was dignified by the term "sexual neurasthenia" It is much more common in the nontraumatic forms and not a little of it is due to the suggestions of "lost manhood" conveyed by certain forms of literature Apparently the prevailing neurasthenic element of "sexual instability" and incapacity is manifest here as elsewhere, and men are more affected than women, seemingly erectile is more affected than the secretory or emission capability Manifestly most of these complaints are entirely subjective, and unless the external parts are flabby and toneless, and the other neurasthenic symptoms are demonstrable, it is inadvisable to regard these claims too strongly Actual impotency from nonorganic sources is so excessively rare that few authentic cases are recorded Subjective complaints of pain and altered sensations referable to the sexual organs are often limited only by the patient's imagination and vocabulary Women occasionally refer to pelvic pain and feelings of aversion regarding the sexual act, but objective manifestations are notably rare

Emissions in either sex are very much rarer than in other forms of the disease Menstruation may become deficient or otherwise altered in rare instances

**A Typical Example**—The symptoms are so numerous and diverse that it would be manifestly impossible to observe all of them in a given case, but a typical instance of the traumatic form usually develops and presents itself in some such way as this A rather "highly strung" but perhaps otherwise perfectly well man or woman is in a collision between vehicles or is hurt in a falling elevator or on a "defective" pavement or stairway The actual physical injury would be diagnosed perhaps as "shock, general contusions and abrasions, and lacerated scalp" At the time of the occurrence there was some dizziness, nausea, and perhaps vomiting, but actual unconsciousness did not occur and the circumstances of the accident were perfectly apparent and readily remembered After treatment by the ambulance surgeon or a short stay at the hospital, the patient returns home alone or by the aid of friends, frequently being able to walk unassisted A physician is summoned and the patient is put to bed, the hospital dressings usually being unre-moved Up to this point there is nothing about the case to differentiate it from another with identical injuries received in some manner that makes the collection of damages unlikely In the case under discussion, however, visits from lawyers, claim adjusters, advising friends, and others soon leads the patient to proclaim various subjective symptoms





patient has not been isolated and complete change of environment can not occur until litigation is ended. Many rehearsals are necessary before the jury appearance, and perhaps also more examinations by experts for both sides, and then the patient goes upon the witness stand and tells as much as is allowed of the preceding and intervening circumstances. By this time the average person is probably much impressed with the gravity of the ailments and may in court exhibit many indications corroborative of the condition, especially if this form of excitement and display brings on violent trembling, agitation, emotion, and perhaps fits or fainting. If the verdict meets anticipations a great source of worry is removed and the patient promptly transfers his attentions from himself to something else and begins to get well. If, however, litigation is prolonged by appeals, the neurosis often continues until this source of suggestion is also removed.

Most of the symptoms begin within a few days, but in some there is an interval of a few weeks during which time the patient may have been at work and apparently well. Some of these cases of late onset bear a close relationship to the advent of not wholly disinterested medical and legal advisers.

Obviously a disease of this sort offers splendid opportunities for the malingerer and faker, and many cases are wholly of this spurious type. There can be no question that many honestly disposed persons are made neurasthenics by the circumstances surrounding our present-day methods of dealing with compensation for injuries, however, that compensation laws do not cure the evil is well shown by pre-war statistics from England and France, which indicate that malingering is largely on the increase, inasmuch as there is a predetermined legal payment during a disability that is asserted or apparent. Soldiers who developed this condition (shell shock) in the World War zone were sent back to the line almost immediately and nearly all of them recovered at once. I saw a number of these cases in World War I at the Evacuation Hospital of which I was commanding officer and there was, as already stated, nothing in their condition dissimilar from the traumatic neurasthenia of civil life.

**Necessary to a Diagnosis**—It is not enough, as already indicated, to take the patient's say-so in regard to "nervousness," but an effort should be made to render some of the subjective signs objective. It is not to be forgotten that many persons may have nervous symptoms of a so-called neurasthenic type (notably the cardiovascular group, and tremors) and yet not have the symptom-complex of the condition or enough symptoms grouped to complete the diagnosis.

There is no one pathognomonic sign, but a typical case of a few weeks' duration should show several of the following more or less prominent objective signs:

- 1 *General appearance* is often suggestive, as might be expected of one complaining so constantly and variedly

2 The expression is care worn anxious and not alert especially if headache and insomnia are featured

3 Loss of weight may be apparent

4 Alternate pallor and blushing may appear

5 Tremors of the eyelids mouth chin tongue and fingers may exist jerking of the arms and hands may occur

6 Pulse is variable and at first is likely to be rapid as might be expected on the arrival of a stranger Later it slows down but again becomes rapid this change of rate especially on exertion is quite typical

7 Throbbing of the carotid, brachial and femoral arteries may be visible and palpable When the pulse is first taken at the wrist the jerking of the extremity may be quite marked and rhythmic but this can be stopped by diverting the attention

8 Cold extremities and sweating are quite common

9 Reflexes are lively more so at first than later especially at the knee a spurious ankle clonus is sometimes present The reflexes may be asymmetric

## HYSTERIA

The derivation of the word means "womb," and for a long time the disease was supposed to be associated with and limited to female disorders. This ailment has existed at least since the days of Hippocrates and has been the subject of much controversy. Charcot probably did most to clarify the situation respecting it, and his views are even in this day substantially regarded as correct. He taught that the traumatic form was, in effect, a manifestation of self-hypnosis due to the psychic and physical shock, and that the symptoms were in part determined by the suggestion made on the patient's mind by the nature of the accident and the part of the body injured.

**Definition**—Hysteria is a functional disease of the central nervous system due to a large number of causes, and characterized by mental, motor, sensory and visceral symptoms of such wide scope as to embrace at least some of the manifestations of nearly every other derangement.

**Causes**—These are legion, but the essential element is that the person should manifest the hysteric "temperament" which is ordinarily hereditary. This implies that the so-called *stigmata* or *signs* of the disease pre-exist, and that the outbreak is due to a wide variety of exciting causes capable of inducing manifestations known as the *accidents of hysteria*. In other words, the *stigmata* always have and will continue to exist, but the *accidents* will disappear and can be induced by certain mental and physical stimuli.

No true hysteria can occur unless the person was previously hysteric in type, and to that extent susceptible and liable to its development.

Psychic sources of origin are more potent than physical, and the latter without the former are incapable of inducing it. Susceptibility to suggestion is very prominent, and impressionability and emotionalism are quite characteristic.

Women are oftener affected than men, and it is commonest at the age of puberty and most likely to appear at menstrual periods. All grades of society are involved, but a larger share are provided by the poor and overworked, or the indolent and rich. The Jewish race is especially susceptible, and the Latins more prone than other Europeans.

Any sort of mental or emotional shock may be the inducing essential cause, particularly sudden grief, joy, anger, sorrow, fear, fright, anxiety, worry, distress, catastrophe. Likewise, abnormal stress and strain, or sexual repressions or impressions, and fears and hopes are factors. Religious excitement and the rigid advocacy of cults and sects are sometimes causative, and the active devotees of some of these are by many regarded as hysterics.

**Traumatic** sources of origin are, of course, very numerous, but the essential and necessary element is *fright* or *psychic shock*, and for this reason the sights and sounds of an accident may be provocative even

in the absence of actual physical damage. In this respect, as in many others it differs markedly from the allied neuroses, neurasthenia in which some physical injury is usually a *sine qua non*.

There is no special section of the body when injured more likely than another to produce hysteria nor is there any special sort of violence especially provocative assuming that the elements of fright and psychic shock exist. However the mental impression or suggestion derived from the manner of the accident and the place of the receipt of the violence often determine the hysterical symptoms and indeed certain manifestations can be predicted from a given set of psychic causes and physical results in a properly predisposed subject, by a process of psychoanalysis a topic so prominently brought forward by Freud and his followers in an attempt to fathom symptoms of a more or less hysterical type. For example a blow on the arm may create a strong mental impression and fear of paralysis and by a process of self hypnosis the patient believes the arm powerless and it thus becomes more or less disabled and useless and to all intents and purposes practically paralyzed. The same psychic control of mind over matter may induce other forms of hysteria and an analysis of the manifestations of many of them will show that the condition started from some mental suggestion that is perhaps a repetition of a memory or occurrence rendered fresh and active in the patient's mind by the psy-

mentation is due to carotene or atabrine, the concentration of serum bilirubin is normal and the reaction is indirect. A direct reaction always is a pathologic finding and is commonly encountered in the various forms of obstructive and hepatogenous jaundice. Such a reaction also is present in the latent jaundice at times seen after biliary colic, in acute cholecystitis, in metastatic tumors of the liver and in many cases of chronic and even acute hepatitis. In the presence of a hemolytic process, a direct reaction indicates an associated hepatic or biliary disorder. Little attention from a clinical standpoint need be given to biphasic or delayed direct reactions.

The quantitative determination shows the degree of retention of bilirubin and its fluctuations from time to time. In many instances estimations every few days are necessary to determine whether the jaundice is stationary, increasing or decreasing in severity. In obstructive jaundice due to stone in the common bile duct, the average value for the serum bilirubin is 10 to 15 mg. per 100 c.c. Fluctuations frequently occur and there is a general tendency for the bilirubinemia to decrease. In neoplastic obstruction of the common bile duct, average values are higher, that is 20 to 30 mg. per 100 c.c. Fluctuations seldom occur and the jaundice is persistent. In parenchymatous disease of the liver, the degree of icterus is variable. In some cases, very mild degrees of bilirubinemia are encountered. On the other hand, some of the highest concentrations (70 to 100 mg. per 100 c.c.) encountered are due to this type of disease of the liver. The higher concentrations are indicative of more serious disorganization of the liver. In obstructive jaundice, similarly high concentrations (that is, much above the average concentration) are indicative of an associated hepatic degeneration.

The *icterus index* is a simple and approximate method of following the degree and variations of bilirubinemia in any case of icterus and is used in many laboratories.

*Dye excretion tests* are frequently used in the determination of liver function. Various dyes may be used, such as phenoltetrachlorophthalein, tetraiodophenolphthalein, Bengal red and bromsulfalein. These tests depend on the rate of disappearance of the dye from the blood stream. It has been our custom at the Clinic to use bromsulfalein. We inject 5 mg. of the dye per kilogram of body weight of the patient, remove a specimen of blood in one hour and determine the amount of dye remaining in the blood with a block colorimeter. Normally, little remains in the blood at the end of one hour. The presence of 40 per cent or more indicates a high degree of retention. Various modifications of this technic have been made but I doubt their practical importance. This is one of the best tests of liver function in cases in which jaundice is not present. The presence of jaundice is a contraindication to the use of this test. When jaundice is present, the test merely shows the impairment to be expected, as indicated by retention of bilirubin and furnishes no additional information. The test is to be used in cases

are less usual types of involvement. The paralyzed part dangles limply and an affected arm or leg drops listlessly when raised. In walking, the gait is characteristic, in that the foot of the involved leg dangles along the toes as if the limb were hung on a springless hinge at the knee.

*Spasm* and *tremor* may occur in the involved muscle group, or independently, it is likely to be coarse and jerky and is usually increased by effort (intention tremor).

*Incoordination* of the affected limbs is common, and an ataxia of some grade may exist. The gait is quite likely to be faulty and move-



Fig 54—Hysterical contracture of right upper extremity, showing the arm supported and unsupported. The fingers are clenched, anesthesia is present over the entire limb, atrophy is absent, electrical response is positive. Duration ten years following a trivial blow on the wrist with gradual development of flexion rigidity of the fingers. This latter was also associated with a rigid flexion posture of the elbow, which spread to the shoulder level. An anesthetic was given in 1936 and 1937 to demonstrate that the condition was easily overcome, and it did not recur until the patient left the hospital. He is today on a light work assignment, and is carried as a compensation case. He has been repeatedly examined by neurologists and others, they all concur in the diagnosis.

ments generally may be awkward and attitudinal, this being rather pathognomonic.

*Astasia-abasia* is inability to stand or walk, and is ordinarily an associate of the paraplegic form, the patient, however, may be able to slightly move the lower extremities when lying down. This usually is a temporary occurrence in the course of the disease and may appear suddenly in attacks, it is sometimes referred to as "cerebellar hysteria." I have seen only a few traumatic cases of this variety.

*Contractures* may occur independently or in the paralyzed part (Fig 54), so that a rigid postural attitude is maintained. This is often

is indicative of severe hepatic damage. In acute hepatitis, positive tests may be obtained early (less than two weeks). In obstructive jaundice, the test may become positive at the end of two weeks. In our experience at the Clinic, the test has been found mildly positive in 50 per cent of cases of malignant obstruction and in 25 per cent of cases of obstruction due to stone or cicatricial stricture. Normal results do not exclude the possibility of parenchymatous origin of jaundice.

The *prothrombin time* should be determined in all cases of jaundice, particularly if the disease is surgical, in which case it should be determined during the preoperative and postoperative periods. In the laboratories of the Clinic, the method of Quick, as modified by Magath,<sup>2</sup> is used. With this method, the normal values are eighteen to twenty seconds. Elevation of the prothrombin time may be due to deficient intake, deficient absorption or deficient utilization of vitamin K. Deficiency of intake is seldom a factor in jaundiced conditions. A deficiency of absorption is common in the acholia of jaundice. It also occurs in intestinal disorders such as those associated with sprue. Deficiency of utilization of vitamin K is encountered chiefly in parenchymatous disease of the liver. In this disease, the vitamin K is not converted into prothrombin, and if the damage to the liver is severe, administration of vitamin K will not control the hypoprothrombinemia and its associated hemorrhagic manifestations. The degree of this failure is an indication of hepatic insufficiency. Data accumulated in the past two years indicate that larger doses than formerly employed may be advisable when small doses are ineffective. Vitamin K should be administered in all cases of jaundice, whether or not the prothrombin time is prolonged. This is particularly true in cases in which operation is to be performed and the administration should be continued during the postoperative period.

Another test is the determination of the distribution of *urobilinogen* in the feces and urine. Much of the recent work in this field has been done by Watson and by Steigmann and Dyniewicz.<sup>5, 6</sup> The methods are tedious and complicated but Watson has simplified the procedure to a great extent. Normally, much of the bilirubin of bile entering the intestine is changed to urobilinogen. Much of this is absorbed into the blood stream, passes to the liver and is reconverted to bilirubin. Under normal conditions, 30 to 200 mg. of urobilinogen is excreted in the feces during twenty-four hours. Small amounts appear in the urine (0.2 to 3 mg. in twenty-four hours). Persistent absence of urobilinogen from the feces (and urine) indicates that bile is not entering the intestine, and hence complete obstruction of the biliary passages. This is most frequently seen in cases of malignant tumors but occasionally occurs from a stone impacted in the common bile duct and from complete cicatricial stricture of the bile ducts. A marked increase in urobilinogen in the feces (up to 3,600 mg. in twenty-four hours) is



the same joint is frequently associated. The contraction ceases often in sleep and always during narcosis, which may be induced for a test or treatment. I recall the case of a married woman who wrenched her hip at home by a sudden twist and fall. She was not completely disabled for a week later, and when she then came to the hospital for suspected hip injury there were no objective evidences of injury about the joint except pain on active and passive motion, and she remained abed and was little affected by numerous diagnostic and therapeutic measures. She had several hysteric stigmata. Later her own physician assumed charge of her again, meanwhile having learned that her complete disability was coincident with a marital row. He thereupon threatened her with the daily application of the actual cautery and she promptly got well.

These cases of "hysteric arthritis" are less common than before the advent of x-rays, and fewer of them are now long treated for mono-articular rheumatism, specific, or even tubercular manifestations.

It is well to constantly bear in mind that *pain alone* is never an inflammatory manifestation, and that it cannot long genuinely exist without associated symptoms that soon stamp it as proceeding from physical and not from psychical sources.

Hysteric patches of hyperesthesia may also be found on various mucous membranes, such as the throat, vagina, urethra, and rectum. Some of these give rise to contractions of the adjacent sphincters with many appropriate symptoms.

Many of these hyperesthetic areas are more painful to superficial than deep pressure, and the patient may scream from the slightest touch and yet thrash about in bed without complaint. On diversion, a great deal or all of the pain is absent, and for this reason and others this symptom must have ample corroboration and reinforcement before it is accepted as diagnostic of hysteria. The location of the injury frequently determines the site of the pain, and it is thus likely to simulate a neuritis or rheumatism in injuries to the extremities or the back, and in the latter region lumbago has to be differentiated also.

These patients claim much suffering and yet they do not look haggard or worn, and they sleep and eat well and maintain a good general appearance, and all of them exclaim most when the audience is of their seeking or to their interest.

**PSYCHIC FORM**—*Emotional manifestations* are very common, and these may show extreme or all modifications between exaltation and depression, joy and sorrow, laughter and tears. The well-known "attack of the giggles," or "spells of weeping," or "fits of anger," or "fainting spells," and other evidences of the play of emotions may occur.

*Introspection and impressionability* are quite characteristic. *Memory deficiency* is quite often asserted, and this is so marked and

is necessary that the presence of these metabolic diseases, as well as that of diabetes mellitus and nephrosis be excluded. Hypolipemia is also encountered in sprue and certain rare diseases of the pancreas.

Elevation of the concentration of *blood urea* may occur if involvement of the kidneys develops in the course of disease of the biliary tract or liver. Occasionally, a lowering of the concentration of blood urea occurs in cases in which long-standing and chronic disease of the liver is approaching its terminal stage. Lowering of the concentration of *blood sugar* and associated hypoglycemic symptoms occasionally may be found in cases of chronic disease of the liver in the absence of any demonstrable pancreatic disorder. The concentration of *serum calcium* may be lowered in chronic obstructive jaundice, such as that due to cicatricial stenosis of the common bile duct. This apparently is due to deficiency of absorption of calcium caused by the acholia. Osteoporosis and spontaneous fractures (particularly of the vertebrae) are usually accompaniments. The concentration of *plasma chlorides* and the *carbon dioxide combining power of the plasma* are altered in cases of external biliary fistula especially if the fistula is complete or nearly complete, and in cases in which cholestasis is present. Dehydration, hypochloremia, acidosis with their accompanying symptoms ensue.

Several *serologic tests* based on alterations of the blood proteins, particularly the globulin fraction, have been developed. These include the Takata-Ara, the colloidal gold, and Hanger's cephalin-cholesterol flocculation tests. Only the last-mentioned test has any support at present. It has been advocated as a means of distinguishing obstructive jaundice from parenchymatous jaundice but these claims have not been substantiated. There is some evidence that it may be of some value in the estimation of the activity of hepatic disease.

The laboratory procedures and tests of liver function that I have mentioned are the ones that we have commonly employed at the Clinic in the past few years. It is still our firm conviction that the diagnosis and management of diseases of the biliary tract and liver are largely based on clinical grounds and that the results of the various tests are rather limited in value. The tests do not distinguish obstructive jaundice from hepatogenous jaundice although they may furnish some assistance in such distinction. They do not distinguish acute disease of the liver from the chronic type. They do not indicate the cause of cellular disintegration. However, some estimate of functional capacity of the liver in several respects can be made from data afforded by several of the tests, particularly with their judicious repetition. They afford some aid in following the clinical course of disease of the liver, in determining the risk of surgical procedures, in directing preoperative and postoperative treatment and nonsurgical treatment, and in evaluating the prognosis. Although these tests have limitations, the data obtained are usually significant. Interpretation of results may be difficult, especially if deviations from normal are slight. Positive

arms and legs and other parts of the body, which move in a more or less *tonic* convulsion. Efforts at restraint are resisted by almost prodigious strength as the patient grasps, pushes, shoves, bites, claws and contorts about. The eyes are usually staring, open and rolling, and the antics may seem well directed and designed for an unconscious person. All sorts of poses and poises may be assumed and at times the body may rest on the head and heels (*opisthotonos*), or the reverse (*emprosthotonos*). The pupils are usually equally dilated. Respiration may temporarily cease long enough for cyanosis and great lividity to occur and the pulse may be rapid from the exertion. These rather slow motions of the limbs and other parts of the body may later become very rapid (*clonic convulsion*) and appear on one side or both and be epileptoid in appearance, but actually there is no such entity as hysterio-epilepsy.

Such a procession may progress with an acrobatic display or a series of remarkable contortions and attitudes more or less sexually suggestive. The duration of the "fit" may be a few minutes or an hour, and end only when physical exhaustion appears, and they may again recur after a period of sleep. There is never absolute unconsciousness in such a seizure, and it can often be aborted by various forms of stimuli, of which may be mentioned smelling salts, ammonia, pressure on the supra-orbital or intercostal nerves—"the gridiron treatment," or the application of vigorous slaps to the soles—"the policeman's tattoo." Pressure on a hysterogenetic zone or an electric shock may also be effective. The nausea and vomiting induced by a hypodermic of apomorphine is not only curative but also has a powerful deterrent value. Mental suggestion in the form of verbal threats, promises or entreaties may stop some "fits." If the audience disappears, the attack often spontaneously subsides. Bystanders may be kicked, bitten or scratched, but the patient is rarely self-harmed. Sometimes a period of delusion or hallucinations may follow, but generally the attack ends as suddenly as it began. The extraordinary poses and attitudes seen in some types of hysteria are rare in the traumatic forms, and, indeed, they are unusual in all forms in this country.

Recurrence is likely, and the patient can often induce an attack at pleasure, and many of them are able to ward off an attack by auto-diversion or will power. After the seizure the patient is usually as well as ever, but occasionally a period of so-called "hysteric coma" may appear, and in this condition the patient may arrive at the hospital, some professional "fit throwers" always become "comatose" on the arrival of the ambulance, but they speedily revive if the surgeon in attendance recognizes them and threatens a police cell and not the anticipated ward bed.

Occasionally the "spell" is followed by motor or sensory paralysis of one or more limbs, or if these have preceded the attack, they may

# CONSTITUTIONAL HEPATIC DYSFUNCTION

MANDRED W. COMFORT

FROM time to time, cases of mild acholuric jaundice, in which hemolytic, hepatic or biliary tract disease is suspected as the cause, are encountered. The abdomen occasionally has been opened without finding disease of the biliary tract or of the liver, and splenectomy, cholecystectomy, cholecystostomy or even choledochostomy has been performed without relief of the jaundice. Medical measures that are used in treatment of hepatic disease likewise have not relieved the jaundice. More recently, jaundice of this type has been the cause for contemplated dismissal of men from the armed forces of our country.

Actually the jaundice in these cases is not due to disease of the blood, liver or biliary tract but apparently is due to an abnormally high threshold for excretion of bilirubin formed at the usual rate. The concentration in the serum reaches 10 to 12 mg. per 100 c.c., and the van den Bergh reaction is indirect. The jaundice is acholuric in type since bilirubin that gives the indirect van den Bergh reaction is not excreted by the kidneys. It is presumably due to an inborn deficiency of the hepatic cells especially with respect to the excretion of bilirubin. The terms "simple familial cholemia," "simple chronic icterus," "familial cholemia" and "familial nonhemolytic jaundice" have been applied to the condition<sup>7-10, 15</sup> but at the Clinic we prefer to call it "constitutional hepatic dysfunction" because this term indicates the constitutional nature of the condition as well as the organ now believed to be responsible.

The jaundice may not be noted before examination or may have been apparent continuously or intermittently for years. It may begin at any age and often several members of a family are affected similarly. The patient may be extremely healthy and vigorous but he frequently complains of lack of endurance and symptoms of the functional type. He may give a history suggestive of cholecystic disease, with or without stones. Physical examination usually does not disclose abnormalities other than a slight icteric tint to the scleras. The liver and spleen are not enlarged and, as mentioned previously, the urine is free from bile pigment (acholuria). The level of serum bilirubin is increased and the van den Bergh reaction is indirect. The results of morphologic examination of the cellular elements of the blood are normal, as is the fragility of the erythrocytes to hypotonic salt solution. The excretion of urobilinogen in feces for twenty-four hours is said to be normal or slightly decreased.<sup>5</sup> Other tests of hepatic function have not disclosed dysfunction of the polygonal cells other than that related to excretion of bilirubin. Although roentgenograms of the gallbladder made by the Graham-Cole technic usually disclose normal function, they may dis-

to squint and ptosis (usually unilateral) Diplopia may also infrequently appear Pupillary changes amounting to sluggishness may occur from muscular tire, but the Argyll-Robertson pupil is never hysteric in origin

*Hearing*—This deficiency also is an anesthetic defect, and is usually found on the same side as the anesthesia or paralysis It is rarely total, and ordinarily is unilateral, presenting impairment alike to bone and air conduction, and thus differing from pathologic deafness It is less common than, but infrequently corresponds and is associated with, the visual contraction, and while these patients have no structural deficiency, yet they do not actually hear It is generally accompanied by anesthesia of the drum, external meatus, auricle, or other parts of the ear

*Speech*—This may be associated with visual and hearing difficulties and is wholly psychic, and ordinarily means that the muscles connected with phonation are paralyzed, spasmodic or anesthetic Such patients can make sounds, but are ordinarily incapable of articulation This aphasia is usually sudden in onset, and may precede, follow or be associated with other hysteric manifestations Paralysis of the vocal cords, and pharyngeal and laryngeal anesthesia can usually be demonstrated, and hoarseness or peculiar vocal sounds are often present Dog bites frequently suggest hydrophobic symptoms, like barking, whining and salivation A number of cases occurred in soldiers as manifestation of "shell shock," with mutism as a prominent feature

*Smell and Taste*—There may be unilateral impairment of one nostril or a symmetric portion of the tongue, and then the corresponding portions of the mucous membrane of the nose, lips and tongue are respectively anesthetic This combination may exist alone, but usually is found associated with visual-auditory defects corresponding to anesthesia or paralysis of the same half of the body This loss of smell (anosmia) and taste (ageusia) are obviously wholly subjective symptoms and hence difficult to demonstrate by tests, if, however, unusual or often vile smells and tastes produce tears or saliva, the degree of impairment is at least not very complete

*VISCERAL FORMS*—Any organ of the body may be involved enough to suggest at first a true lesion, and the differentiation is made by the complex of symptoms and the presence or absence of hysteric stigmata Many of the manifestations are often quite neurasthenic in type

*Heart involvement* may be represented by alterations in pulse rate and attacks of precordial pain resembling angina pectoris

*Blood vessel involvement* may be suggested by cyanosis, edema, peculiar rashes and blushes, and other surface manifestations, of which dermatographism (tache cérébrale) or urticaria are typical Hysterics, rule, do not readily bleed, probably due to spasm of the coats of

dysfunction of the type seen in constitutional hepatic dysfunction exists in chronic hemolytic icterus.

### INCIDENCE

The true incidence of the disease among patients who register at the Clinic probably is much nearer the average of thirty per year, as reported in 1935, than the average of four per year, as reported in 1944. The incidence in the latter report would have been greater if the records had been examined of all cases in which the concentration of serum bilirubin with an indirect van den Bergh reaction was greater than 2 mg. per 100 c.c.; this was done in preparing the 1935 report.

### DIFFERENTIAL DIAGNOSIS

The recognition of constitutional hepatic dysfunction as a distinct clinical entity is important, not because it affects the health of the individual but because a correct diagnosis avoids the erroneously serious prognosis of true hepatic disease, prolonged medical treatment and unnecessary surgical treatment. The diagnosis would be made more often if all abnormally high elevations of serum bilirubin with an indirect reaction were examined more critically and if the concentration of bilirubin and the indirect or direct nature of the van den Bergh reaction were determined whenever the patient complains of slight jaundice, biliousness, liverishness and sallowness.

The diagnosis of constitutional hepatic dysfunction should be made only after the presence of hemolytic and hepatic disease has been eliminated.

Hemolytic disease is excluded by the absence of history of exposure to toxic, infectious and parasitic agents with hemolytic properties, by the absence of anemia and splenomegaly and by normal morphologic examination of erythrocytes, normal fragility of erythrocytes to hypotonic salt solution and normal excretion of urobilinogen in the urine and feces. Occasionally splenomegaly occurs in a case that otherwise conforms to the definition of constitutional hepatic dysfunction but the latter diagnosis should not be made without further observation and study because of the possibility of atypical hemolytic icterus.

Most types of jaundice due to hepatic disease are excluded at once by the indirect nature of the van den Bergh reaction. The various hepatic functional tests further serve to exclude other dysfunction of the hepatic cells and, inferentially, disease of the hepatic cells. Only when the serum bilirubin responsible for latent jaundice of hepatic disease gives the indirect van den Bergh reaction is a differential diagnosis necessary. Slight latent jaundice due to serum bilirubin giving the indirect van den Bergh reaction often precedes the jaundice of hepatic disease with its more characteristic direct van den Bergh reaction, and may persist for months and even years after recovery from profound damage to the hepatic polygonal cells and after other

The extremes of age offer poorer prospects than the adult type. Women are apt to recover as quickly as men, in hysteria, males usually get well more promptly than females.

2 The Environment—If the subject can be isolated and freed from the attention of would-be advisers, the outlook is excellent. Tact on the part of the physician and others is extremely important, and the habit of optimism is nowhere more needed than in these ailments.

If the physician finds that the patient no longer imposes entire faith and confidence in him, his value is so lessened that he had better retire.

The *prospect of litigation*, as indicated, is a marked deterrent to recovery, and even in genuine cases serves to keep the patient alert and alive to every change in symptoms. It is a constant source of worry and expectation and is probably as potent a factor as any in determining the outcome. Patients rarely recover while adjustment is pending, but the vast majority of them respond promptly when it is accomplished, and nearly all of them get well soon thereafter.

I have known of a case of a woman about fifty years old who had very marked evidences of major hysteria, and her trial was hastened in view of affidavits made by her attending physicians to the effect that she was soon likely to die. She was markedly emaciated and had well-defined contractures, with hemiplegia and hemi-anesthesia of the left side. Her voice was almost inaudible and she had numerous hallucinations and trances of a religious type. Originally she had fallen from a trolley car, and the onset of her hysteric manifestations was associated with injuries to the back and legs which induced the suggestion of paralysis. She had been abed some four months when I saw her, and by starvation had become exceedingly weak. Her claim was adjusted and within a short time she was reported as having resumed her regular duties. Theoretically the outlook was bad in this instance, considering her age, environment, and a weakness greater than I had hitherto witnessed in a similar case.

I once examined a young Negress who had been in a collision of cars and who had received a few contusions of the scalp and other parts of the body. She promptly went into a trance on reaching home, and one arm and leg were anesthetic enough to permit her to be made "a human pin-cushion." Her doctor sensed the situation and stopped the "trance" with a siphon of aerated water, but she was anesthetic and abed when I saw her a few days later. Immediately after adjustment her doctor told me she got well enough to go to Coney Island on part of the proceeds. The first of these cases had received unremitting care from four doctors, two nurses, and many relatives, and day by day her condition got worse from too much attention. The second case was a splendid subject or "medium," and under different management was capable of developing almost any set of hysteric symptoms.

e and Extent of the Injury—How the accident happened and

gave negative results. The concentrations of serum bilirubin were 3.0 and 1.6 mg. per 100 c.c. and the van den Bergh reaction was indirect.

The diagnosis was constitutional hepatic dysfunction. The patient recently reported by letter that the episodes of icterus still occurred two or three times a year but that otherwise he had been getting along well.

*Comment.*—The jaundice in case 1 was familial. It was chronic and latent most of the time but overt at intervals when its depth was increased by nervous and emotional factors. Although the attacks had occurred for forty years, they apparently had not affected the patient's health or diminished his endurance, and had not led to the development of disease of the blood, liver, spleen or biliary tract. This case emphasizes the effect of nervous and emotional stress on the depth of the jaundice, an effect that long has been recognized.<sup>1, 5, 6, 12</sup> The jaundice that occurs after renal colic must be explained on a similar basis.

CASE 2.—A man, aged thirty-five years, registered at the Clinic in June, 1938. Except for thyroidectomy in 1930 and appendectomy and tonsilleectomy in 1937, his health had been good. His endurance was satisfactory and fatigue occurred only after long periods of intense work. About six months prior to registration the patient had had a short period of malaise with slight jaundice and some loss of weight. The jaundice had persisted after the malaise disappeared and had fluctuated in intensity. Several doctors had diagnosed the condition as acute hepatitis or catarrhal jaundice. A high carbohydrate diet and various medicines including calcium, vitamin B and dilute hydrochloric acid had been prescribed.

The results of general physical examination were essentially negative with the exception of slight scleral icterus. Urinalysis and routine serologic test for syphilis gave negative results. The hemoglobin was 15 gm. per 100 c.c.; erythrocytes numbered 4,900,000 and leukocytes 8,100 in each cubic millimeter of blood. The erythrocytes were normal in size and shape. Fragility of the erythrocytes to hypotonic salt solution was normal. Gastric analysis after a test meal showed free acidity. Roentgenograms of the thorax, gallbladder and stomach were negative. The basal metabolic rate was -3 per cent. The concentration of serum bilirubin was 2.0 mg. per 100 c.c. and the van den Bergh reaction was indirect. Brom-sulfalein test of liver function did not disclose retention of dye.

The diagnosis was constitutional hepatic dysfunction.

The patient was not aware that other members of his family were similarly affected but on inquiry on his return home he found that his brother had a more yellowish tinge to his eyes than the patient. He also learned that his father's family was noted for the yellowish tinge to their complexions, some members of the family having this to a marked degree. His maternal antecedents were fair skinned and there was no history of jaundice among them.

*Comment.*—Case 2 again illustrates that constitutional hepatic dysfunction is compatible with excellent endurance and health. The jaundice was discovered when the patient was thirty-five years of age, and then only because his physician was a careful examiner. Concern about the jaundice was only natural and treatment for hepatitis was without benefit. The patient's anxiety was dispelled when the nature of the condition was explained and only on inquiry was the familial incidence of the condition established.



2. *Local Management*—*Pain* and *insomnia* will be the two chief symptoms requiring aid. It is to be remembered that a hypodermic of morphine is no more potent to the hysteric than sterile water, in fact, the latter is far more efficacious if administered with the dramatic detail so craved by such a patient. Therefore the relief of these and other allied mental symptoms must be largely by mental means.

*Pain* is treated by various external applications, hot or cold. The local use of the cautery is very effective in humbug and allied pains. Electricity, massage, baking, and hydrotherapy all have their place. It is unwise to rely on drugs, as they may prove habit inducing and at best soon lose their effect. It is especially harmful to use the hypodermic with these imitative people.

*Insomnia* is best relieved by nightly warm baths or spongings, or by cold compresses to the forehead or nape of neck. A brisk body massage is quite effective in some cases. The suggestion that sleep will result after a planned treatment is part of the therapy.

*Paralyses* and *contractures* require no special treatment aside from massage, vibration, and electricity, but these must not be resorted to if they tend to aggravate existing symptoms or suggest others. Hypnotized and anesthetized patients are sometimes permanently relieved of these symptoms by thus demonstrating their non-physical existence.

*Special sense defects* are given the benefit of the suggestion implanted by electric or other forms of local treatment.

*Convulsions* are sometimes cut short by pressure on hysterogenetic zones or other painful areas, such as the supra-orbital or intercostal regions. Many fits stop just as soon as the audience departs. These attacks rarely harm the patient, and thus they can be disregarded. Vigorous use of cold or hot water or spirits of ammonia cut short many of them. A jet from a siphon of aerated water or a hosepipe is quite effective. The hysteric will not have a "spell" unless the surroundings are comfortable, and thus the environment again plays a prophylactic as well as a curative part. A girl with "highsterics" is less likely to encore her exhibition if the only applause is an old-fashioned spanking or a session alone in her room without food.

If "the punishment fits the crime" there is usually little necessity to again prove its deterrent value.

Many of these people run the gamut of all sorts of treatment, and finally derive much benefit from adherence to some cult or "istic" belief. Shrines, relics and meccas from earliest times have thus worked wonders by faith and suggestion when all else has failed. The discipline and fixed attention of Christian Science may act admirably in such a "mind disease," there is no question that "cures" and various "pathies" are active agents in some cases. Hypnosis should be used with great care. Hysteria may be induced or cured by the emotional strain of a religious "camp meeting" or by similar dramatic appeals.

since otherwise he would not consult a physician. Such complaints are usually functional but may be of some other type. It is not certain that the fatigue and lack of vitality so frequently complained of are due to the condition.

As previously mentioned, the liver was normal in the one case in which biopsy has been performed.

### TREATMENT

Whether treatment of constitutional hepatic dysfunction is indicated is questionable since it apparently does not affect the general health. Treatment such as is given in disease of the liver is disappointing and is not indicated. Cholecystectomy, choledochostomy and splenectomy have no influence on the course of the jaundice or on the functional complaints of the patient. Operations on the biliary tract are indicated only when bona fide disease of the gallbladder or calculous disease of gallbladder or ducts exists. Avoidance of precipitating stresses such as overwork, fatigue and emotional and nervous stress may lessen the depth and the frequency with which increases in depth of jaundice occur.

### COMMENT AND SUMMARY

Attention is again called to constitutional hepatic dysfunction, a condition in which jaundice is due to an inborn inadequacy of the hepatic cells, particularly with regard to excretion of bilirubin. Its sole clinical manifestation is acholuric jaundice. The jaundice may be latent or overt. The essential pathologic finding is an increase in serum bilirubin giving an indirect van den Bergh reaction. It is not due to hemolytic or true hepatic disease or disease of the biliary tract. The prognosis is excellent. Its recognition is important to prevent an erroneously serious prognosis and unwarranted medical and surgical treatment.

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*Subjectively*, complaint is oftenest made of pain, weakness, insomnia, anorexia and impaired genito-urinary functions

*Pain*, if real and prolonged, inevitably shows in the countenance and general appearance of the bearer. By resort to the "relocation test" the actual persistence of pain can be determined, and the malingerer cannot accurately relocate spots previously marked as painful to pressure. A zone that is tender is moved with care and is suitably protected during every action, but the malingerer forgets this when taken off his guard, for example, a back "too painful to move" is readily bent when a request is made to remove the clothing or shoes. Painful spots on the scalp and elsewhere will stand considerable pressure if the attention is elsewhere focused by identical pressure, in other words, a malingerer's pain is not consistent or persistent and is out of all proportion to the severity of the original physical damage.

*Weakness*, if real and continuous, means flabby muscles and general lack of tonicity, the faker is not infrequently of athletic type.

*Insomnia* shows in the face and cannot long honestly exist without giving objective signs.

*Anorexia*, if real, means malnutrition and generally atonicity of the stomach, with demonstrable tympanites and other signs.

*Impaired genito-urinary powers* show in flabby external parts, and when urinary action is abnormal the urine will be concentrated and perhaps otherwise altered.

Sexual claims are limited only by the imagination and verbal capacity of the patient and are manifestly hard to disprove, but lasting diminution of this sort is very rare even in profound neuroses. Lively cremasteric reflexes are usually incompatible with sluggish sexual functions.

*Objectively*, complaint is oftenest made of lameness and stiffness, paralysis (muscular or sensory), tremor, convulsions and special sense defects.

*Lameness* and *stiffness* have usually a demonstrable source and are very rarely the only symptoms of real injury. Ordinarily they are claimed in association with or following an injury of the back, or to a joint, notably the ankle, shoulder, knee and hip. At first the malingerer asserts that the part cannot be moved at all on account of the lameness or stiffness, but later most of them will admit some motion at least. This is especially true in the shoulder, where it is often asserted that motion to a right angle is possible, but not beyond. Many of these cases are immediately disproved when the joint is noted to function freely while the clothing is being removed. Nearly all of these patients voluntarily hold the joint rigid during attempts to move it further than they desire, and this purposeful contraction is never twice alike and is much too general to indicate involuntary spasm of muscle. Flabbiness of muscle and alteration in the appearance of the joint inevitably fol-

# DIFFERENTIAL DIAGNOSIS OF NEPHRITIS

MELVIN W. BINGER

THE disease commonly known as glomerulonephritis presents many varied and interesting problems in etiology, differential diagnosis and treatment, and it is the purpose of this paper to consider some of these problems.

The disease, as first described by Richard Bright in 1827, was but vaguely understood and even now, more than one hundred years later, there are many aspects of the disease that are largely a matter of conjecture.

The disease presumably is due to an inflammation or toxic reaction of the capillary loops of the glomeruli, which is really an endocapillaritis and an involvement of a part of the vascular system. In the acute form it very frequently is associated with or follows infections of the upper part of the respiratory tract, tonsillitis, scarlet fever and other infectious processes. It has been determined by various investigators, and from our records at the Clinic, that in about 85 per cent of cases of acute glomerulonephritis the disease is attributable to infectious processes. It is hard to conceive that the organism causing the primary respiratory or other infection is transmitted by the blood and lodged in the kidneys, thus producing the glomerular changes. It is thought rather that toxins from the primary infection are the causative factor. The possibility of a virus exists and many investigators have considered an allergic reaction as the cause of the glomerular changes.

However, it is not my purpose to go into minute detail regarding the etiology and pathology and treatment of glomerulonephritis, but rather to consider the differential diagnosis of glomerulonephritis and suggest some of the common pitfalls in the diagnosis of this disease.

To make a diagnosis of glomerulonephritis solely on the presence of albumin and blood and casts in the urine is a hazardous procedure and may result in the wrong diagnosis, for many other disorders in the body may produce abnormal urinary findings.

*Polycystic kidneys* will produce the identical clinical picture of chronic glomerulonephritis and the differential diagnosis frequently is not easy, especially in cases in which the patients are obese and the concentration of blood urea is increased. The obesity makes palpation of the kidneys difficult and, if the value for the blood urea is more than 70 or 80 mg. per 100 c.c., intravenous urography is not a satisfactory method for outlining the kidneys as the iodine compound is not sufficiently concentrated to be visualized on the urogram. Retrograde pyelograms can be made, but always with some hazard. However, the size of the kidneys frequently can be outlined on the roentgenogram. If the value for the blood urea is normal or nearly normal,

and observing the response True lost sensation is rarely the sole evidence of injury, and when asserted as the only manifestation must be regarded with suspicion Actual loss of sensory power presents no contraction, twitch or reflex action on stimulation, the malingerer braces for the expected attack, but the examiner will eventually gain some response in assumed cases Electric stimulation is another means of showing the real from the false Many persons are insensitive to ordinary superficial pain either naturally or from training, and some of this may have developed from the schoolboy trick of transfixing a fingertip with a pin or needle

*Tremor* in the malingerer always gets worse when observation is expected, but if it is deliberately watched, the rate and extent of it will vary within wide limits and soon cease from fatigue The assumed tremor of fingers will often promptly stop or markedly vary if the malingerer is asked to demonstrate it by holding the arm out straight. Likewise, twitching, jerking, grimacing and more or less choreiform motions will vary so much and so often that even the perpetrator of them may soon admit "they are worse at some times than others" The signature of a malingerer may be perfectly legible even though continuous jerking of the hand is alleged A great many tremors are alcoholic

*Convulsions*, fits and other "spells," "attacks" and "seizures" are largely matters of convenience, and they are never attended by real unconsciousness nor does the facial appearance vary much The pupils normally react, and any change of pulse and respiration is produced by exertion Professional "fit throwers" and "dummy chuckers" are less common than formerly, largely because they find it does not pay, even the tyro ambulance surgeon recognizes them, and they go to jail or the psychopathic ward and not to the expected hospital bed

*Special sense defects* usually refer to aphonia and deafness, but these rarely last long and are easily disproved

2 NEUROSIS PLUS MALINGERING—These are the cases presenting some objective neurasthenic or hysteric signs, with many subjective claims that cannot be legitimately ascribed to them

I am aware that exaggeration and perhaps even deception are part and parcel of hysteria, yet the cases I have in mind are not of a grave enough sort to develop these as part of their hysteria Such a case may show some tremor, instability of muscle and the circulatory apparatus, and perhaps even have a few areas of anesthesia, and give the history of emotional upsets, and perhaps even an occasional "hysteric convulsion" At the time of the examination a host of dissociated subjective claims will be made but the examination reveals practically nothing Most of these patients are natural hysterics trading on their newly discovered deficiencies and are virtual malingerers so far as disability is concerned

recognized more and more as an important diagnostic aid in cases of hypertension and chronic glomerulonephritis, to be sure that one is not dealing with atrophic pyelonephritis. I know of no situation that gives me more satisfaction than to find, and have removed, an atrophic kidney in a case in which the patient seemed doomed and, by this surgical procedure, restore a patient to health.

A condition that somewhat resembles atrophic pyelonephritis is *congenital hypoplastic or malformed kidney*, which may or may not produce hypertension and diffuse vascular changes. If hypertension is detected in a child, urologic studies should be made to rule out the presence of a unilateral hypoplastic kidney. If such a kidney is found, its removal should be seriously considered. This condition can and will produce the clinical picture of malignant hypertension.

*Tuberculosis of the kidneys* or of a single kidney may be confused with chronic glomerulonephritis, and, when pus and blood, as well as albumin, persistently occur in the urine, a centrifuged specimen of urine should be stained for *Mycobacterium tuberculosis*. If any doubt exists about the presence of this organism, guinea pigs should be inoculated. Excretory urography and cystoscopy are of immense diagnostic help. Fortunately, tuberculosis usually affects only one kidney and, if the involved kidney is removed, the chance of recovery is good. At present, chemotherapy does not seem to be of much value in this disease.

*Hypernephroma of the kidney* may produce albumin and blood in the urine. Usually, there are recurrences of gross blood in the urine. The malignant lesion may be far advanced before there is any clinical indication of its presence and I have seen cases of widespread metastasis in which the primary source was found by urologic studies. If the hypernephroma is discovered and nephrectomy done early, and if deep roentgen therapy is employed subsequently, the immediate outlook is favorable.

*Adenomyosarcoma*, or Wilms' tumor, in children may present the clinical picture of hypertension and nephritis. However, it is rarely encountered and the outlook is invariably poor. Urologic studies should be carried out in cases in which the presence of this tumor is suspected.

In the advanced stages of *essential hypertension* it is quite difficult or impossible to tell by the findings alone whether the primary condition was glomerulonephritis or essential hypertension. The albuminuria and sediment in the urine are similar in each disease. The impairment in renal function, the anemia, and the degree of hypertension are confusingly alike in the two diseases, and the end results, such as uremia, cardiac failure or cerebral vascular accident, occur with about equal frequency in the two diseases. In many instances, only the pathologist who examines the renal tissue can in any measure be certain as to which was the primary disease. However, there are certain

# IMPAIRMENT IN EMOTIONAL CONTROL PRODUCED BOTH BY LOWERING AND RAISING THE OXYGEN PRESSURE IN THE ATMOSPHERE

(A Fundamental Relation between Psychic and Somatic Processes)

ALVAN L. BARACH, M.D., F.A.C.P.\*

## INTRODUCTION

TISSANDIER, in 1875, first described in clear and vivid terms the release of emotion due to oxygen-want at high altitude, he recorded his feelings at 26,000 feet during the latter part of the balloon ascent with Croce and Sival as follows

"There is no suffering. On the contrary, one feels an inward joy. There is no thought of the dangerous position. One rises and is glad to be rising."

Tissandier recovered but his companions were dead when the balloon descended. Paul Bert<sup>1</sup> was soon to provide incontrovertible evidence that the symptoms which took place at high altitude were due to a lowering of the pressure of oxygen in the atmosphere. A characteristic disturbance in cerebral function, manifested by impairment in emotional control, reason, judgment and memory, as well as by deficient performance of the special senses, was described as the result of the lowered oxygen pressure in the brain. Heber<sup>2</sup> in discussing the symptoms of the average European at Ladak, Kashmir (11,500 feet), says "Mental deterioration is not as serious, however, as the change in temperament and all subjective functions. It is astonishing how the most decisive of men will slowly and insidiously lose the power of decision and become unwilling to bear responsibility." Barcroft<sup>3</sup> remarked that any prolonged mental effort in Cerro de Pasco, at an altitude of 14,200 feet, involved a degree of fatigue which at times necessitated a trip to the coast to prevent a nervous breakdown. Haldane<sup>4</sup> almost lost his life by urging his assistants to lower still further the concentration of oxygen in an experiment to which he had exposed himself. He was completely disorientated, and, as Tissandier before him, had no thought of the dangerous position in which he was placed.

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From the Department of Medicine, College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York.

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\* Associate Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University, Assistant Attending Physician, Presbyterian Hospital.

hypertension, chronic glomerulonephritis, or other diseases that produce hypertensive vascular disease. It is not common to see uremia in cases of uncomplicated subacute bacterial endocarditis. It is fairly common to see cases of subacute bacterial endocarditis in which repeated blood cultures are negative, and one should not be misled by negative blood cultures.

*Periarthritis nodosum* or diffuse endarteritis produces a myriad of symptoms and clinical findings that may be confused with those of chronic glomerulonephritis. There may be albumin, casts and erythrocytes in the urine, and hypertension and evidence of widespread cardiovascular disease. However, the severity and rapid progression of the clinical symptoms and findings are out of proportion to what one would expect in cases of chronic glomerulonephritis. Usually, the retinal findings are minimal and the evidence of cardiac damage is much more profound in periarthritis nodosum than it usually is in chronic glomerulonephritis. There, too, will usually be peripheral neuritis and pain and soreness in muscles and tenderness along certain arteries, which do not occur in cases of nephritis. If painful nodules along the arteries can be found, the evidence is rather in favor of periarthritis nodosum. A biopsy of a suspected nodule or region will frequently be the deciding clue in the diagnosis. Unfortunately, this disease presents such a widespread and atypical clinical picture that it usually goes unrecognized before death and, more frequently than not, the diagnosis is finally established by the pathologist at necropsy. The legion of clinical findings, the unusually rapid progress of the disease, the widespread organic involvement, the usual leukocytosis, fever, severe cardiac failure and cerebral involvement without definite clinical syndromes should lead one to suspect the presence of periarthritis nodosum.

*Acute disseminated lupus erythematosus* in many ways resembles periarthritis nodosum and subacute bacterial endocarditis and will produce a clinical picture that is easily confused with that of glomerulonephritis. It is thought by some investigators to be a closely related disease as far as the cause, clinical findings and course are concerned. It runs a subacute course with fever, progressive anemia and pronounced leukopenia. There may be pericarditis, arthritis and an erythematous and purpuric rash, usually involving the face but frequently also the extremities. Blood cultures are invariably negative. The protean nature of the clinical picture is thought by some investigators to be due to the widespread vascular involvement.

In *advanced pulmonary tuberculosis* and tuberculous involvement of other organs, the urinary findings, such as albuminuria, casts and hematuria, may be mistaken for those of chronic glomerulonephritis. These findings may result from the toxic effect on the kidneys or from tuberculous lesions of the kidneys. In the latter instance, *Mycobacterium tuberculosis* may be found in the urine. A widespread



mental and physical sluggishness, alternating with short periods of either euphoria or irritability." Observations on the effect of anoxia on mental functioning have been made by other investigators<sup>8, 9, 10, 11, 12, 18</sup>

#### SIMILARITY OF THE EFFECTS OF ALCOHOL INGESTION TO THOSE OF ACUTE ARTERIAL ANOXIA

During the past ten years my colleagues and I have also investigated the effect of breathing atmospheres containing 10 to 13 per cent oxygen on normal subjects and on patients with psychoneurosis<sup>14, 15, 16, 17, 18, 19</sup>. The similarity between the effects of anoxia, produced by lowering the pressure of oxygen in the inspired air, and the consequences of ingestion of alcohol have been observed by many students of the subject. Alcohol is now regarded as a histotoxic agent which produces tissue anoxia<sup>20</sup>. Oxycytochrome is stabilized by alcohol so that the oxygen is not removed at the normal rate<sup>21</sup>. All narcotics, including alcohol, inhibit the oxidation of substances important in carbohydrate metabolism in the brain<sup>22</sup>. Although alcohol is ultimately a depressant, it is well known that there are preliminary periods of euphoria that follow its use. Impairment of emotional control after ingestion of alcohol appears to be similar, if not identical, to that which is produced by lowering the pressure or concentration of oxygen in the atmosphere.

Although the well-being which frequently follows the taking of moderate amounts of alcoholic beverages *seems* to be different from the effects of oxygen deprivation, my observations and the experience of others have inclined me to the belief that there is no essential difference. The chief reactions, in respect to impairment of emotional control, are similar, namely, either *a period of elation and euphoria followed by drowsiness*, or *an initial period of drowsiness, dullness and irritability*. The appearance of feelings of elation is dependent to a very considerable extent on the surrounding environment. When alcohol was taken at 9 A.M. in the presence of a laboratory set-up, the characteristic effects of expansiveness and cheerfulness were often lacking in subjects who took cocktails in the evening under more social circumstances.

In experiments in which male subjects were tested by men in a low pressure chamber, impairment in emotional control was manifested either by euphoria, boisterousness, irritability, pugnaciousness, undue laughter or by drowsiness, lethargy and sleep<sup>5, 6</sup>. In about half of the cases the more boisterous manic mood was observed and in the other half the tendency toward dullness and irritability. This reaction has been observed in subjects exposed to a simulated altitude of 15,000 feet and in a study at 12,000 feet but when experiments were made at a far higher altitude, such as 45,000 feet, the incidence of euphoria was considerably less. Even during the inhalation of pure oxygen at altitudes

will be more than 11 mg. per 100 c.c. and the value for the inorganic serum phosphorus will be less than 3 mg. per 100 c.c. It is probable that in many of these cases the disease escapes diagnosis and is considered as nephritis or other systemic disease.

In further consideration of the condition commonly known as *chronic lipid nephrosis*, one is confronted by the two schools of thought as to whether lipid nephrosis is a variety of chronic glomerulonephritis, or whether it is a degenerative disease of the kidneys and not a manifestation of chronic glomerulonephritis. In my observations of cases of so-called lipid nephrosis, the disease eventually has progressed to typical chronic glomerulonephritis with uremia, hypertension and diffuse cardiovascular involvement. Cases in which severe albuminuria, hypoproteinemia, and edema, hyperlipemia with normal or only moderately elevated blood pressure, and a normal concentration of blood urea are considered as chronic glomerulonephritis with the nephrotic syndrome. The nephrotic syndrome apparently occurs in cases in which the nephritis is benign and in which so much albumin is lost through the urine over a long period of time that the concentration of serum protein is depleted to or below the critical level of 5 per cent, which results in a lowering of the colloidal osmotic pressure and of the blood, resulting in edema. It is not clearly understood why there should be an increased permeability of the glomerular loops, conceding, of course, that the filtration of plasma proteins takes place through this element of the kidneys. Neither is it clear why some patients with the nephrotic syndrome will have a normal blood pressure while others will have severe hypertension and vascular involvement. It is thought to be due to the degree of impairment or unimpairment of blood flow through the kidney, which has been ably demonstrated by Goldblatt and other investigators.

Lipemia is not peculiar to nephrosis alone, for it is frequently observed in cases of proved chronic glomerulonephritis.

In *Hodgkin's disease* and *lymphosarcoma*, the clinical picture of nephritis is frequently observed. There may be albumin, casts and erythrocytes in the urine, as well as renal failure, as evidenced by an increased concentration of blood urea. Blood pressure may also be elevated and anemia may be present. However, the generalized adenopathy, enlarged spleen and frequently the typical mediastinal widening are clues favoring the diagnosis of these diseases. Frequently occurring attacks of fever of the Pels-Ebstein type may be noted. Biopsy of a lymph node is advisable and frequently will establish the diagnosis. It is thought the renal changes are due to infiltration of the kidneys by the malignant process. However, in some cases only toxic changes were noted on microscopic studies. Marked improvement is frequently noted after roentgen therapy. Blood counts and smears are helpful in distinguishing Hodgkin's disease and lymphosarcoma from chronic leukemia, and the microscopic appearance of the

## EFFECT OF PERSONALITY OF THE INDIVIDUAL ON RESPONSE TO ANOXIA

In addition to the effect of environment on the type of impairment of the inhibitory impulse, there is the basic factor of the personality of the individual himself. I have had the opportunity of observing carefully men exposed both to alcohol and to low oxygen atmospheres, in which the response has been similar in each instance. One man consistently boasted of his mental and investigative ability, revealing a manifestly exaggerated self-esteem. In this individual, exposure to the presence of a woman had not shown any special change in behavior. In another case, however, the personality showed no perceptible alteration in self-esteem. A logical conversation was conducted for half an hour and the subject himself asked whether he had shown any change in personality. I freely admitted that he had talked about the problem under discussion as normally as I would have expected him to do at sea level. However, when a nurse was brought into the environment, the subject began to laugh, slap his hand on his thigh, and then give way to uncontrollable hilarity. The consistently different behavior on the part of these two men made clear that the type of impairment in emotional control which is the result of anoxia is also determined by the personality of the man himself.

In a series of sixteen subjects tested at an altitude of 15,000 feet for one and three quarter hours, one individual consistently showed marked aggressiveness. In the group in which dullness and drowsiness took place from the start, the impairment of emotional control was manifested in irritability when instruction or criticism was made. In one of the sixteen subjects referred to above, the degree of drowsiness was so marked as to suggest that the individual had a poor tolerance to altitude anoxia.

It is of considerable interest to note here that in five of nine psychoneurotic patients the efficiency of intellectual response was better after inhalation of 13 per cent oxygen for three hours, despite serious impairment of emotional control. These patients showed less preoccupation with their symptoms, and in that way revealed an emotional relaxation similar to that which ingestion of alcoholic beverages sometimes induces. It was apparent in psychoneurotic subjects that psychometric tests are less valid in estimating the integrity of the personality than is the appraisal by the investigator of latent impairment in emotional control. A normal individual at rest in a low oxygen atmosphere may manifest no special disturbance in affective behavior until he is challenged by some unusual remark. If a man under such conditions is asked whether he is the handsomest man in the group, embarrassment, flushing of the face and uncontrollable laughter may suddenly take place. Similarly, an individual may be doing his task reasonably well until a remark is made, such as that he is doing less well than one of his competitors, at which time anger and irritability may become sufficiently

## CHRONIC CERVICITIS

MONTE C. PIPER

CHRONIC cervicitis may include erosion of various types and degrees, chronic cellulitis and fibrosis, cysts, polyps, lacerations with infection, eversion and malignant changes.

Symptoms resulting from chronic cervical involvement may be purely local or more extensively systemic. There is individual variation in the degree of distress. Rather extensive involvement of the cervix may produce surprisingly little discomfort in some cases and the diagnosis may be determined only by examination. In others the involvement may be mild but may seem to produce symptoms of an unwarranted severity.

Leukorrhea usually accompanies any degree of chronic cervicitis and is the most frequent finding. Pelvic weight or heaviness is often aggravated by fatigue and, if the paracervical ligaments are much involved, may result in actual pain. Dyspareunia may be complained of. Menstrual irregularities or abnormalities and increased dysmenorrhea sometimes accompany chronic involvement. Metrorrhagia should lead to careful search for any possible early malignant process. Sterility is sometimes corrected by eliminating cervical lesions.

More remote symptoms are most frequently complained of as urinary distress. The close proximity of the ureters and base of the bladder to the network of lymphatics, vessels and nerves surrounding the cervix explains the frequency of urinary complication. Both infections and neoplastic processes may readily invade the region of the bladder and the ureters by direct extension.

The history of a patient who has chronic cervicitis may be clarified by a frequent review of the salient points. Frankly discussing with the patient her ideas about her symptoms and explaining to her the findings and their probable significance will help to encourage her confidence and to manifest the physician's understanding of, and sympathy with her in, her problem. Some women hesitate to tell their story completely at first and it may happen that the patient will divulge her innermost fear only after treatments are completed and at the time of dismissal. Her chief anxieties may be summed up in the fear of having some loathsome disease, of development of a malignant lesion or of an inability to perform her normal sexual functions. The history should record duration, remissions and previous therapeutic attempts.

Pelvic heaviness or pain usually is responsive to the application of heat, to rest and to some of the more common analgesics. Back pain in the sacrolumbar region often accompanies cervicitis and its relief may follow elimination of the cervical involvement. It is fairly frequent for a patient to state that a chronic backache has been relieved in a

in emotional control is the result of *acute* anoxia, but further studies are warranted to determine whether repeated exposure to moderate anoxia results in a clearly apparent neurotic disorder

#### IRRATIONALITY PRODUCED BY INHALING 50 PER CENT OXYGEN IN INDIVIDUALS WITH CHRONIC ANOXIA

Since 1920 I have taken part in a series of investigations on patients with acute and chronic anoxia treated with oxygen-enriched atmospheres. When oxygen therapy is responsible for the relief of oxygen-want in acute disturbance of pulmonary or cardiac function, lessened dyspnea and delirium, and increased tendency to sleep have been frequently noted, but no disturbance in affective behavior has been seen. The decreased delirium observed in patients with pneumonia<sup>27</sup> has been interpreted as a result of the increased tendency to rest and sleep afforded by relief of dyspnea rather than as a specific effect of oxygen on brain function. The inhalation of 20 per cent oxygen and 80 per cent helium in patients with intractable asthma is also at times followed by deep sleep, as a result of relief of the physical effort of breathing. The response of patients with chronic anoxia, however, shows a striking difference.

In those cases of pulmonary emphysema in which pre-existing arterial anoxemia has been present over a considerable period of time, the continuous administration of 50 per cent oxygen may result in a swift impairment in emotional control, proceeding to delirium in some instances.<sup>28, 19, 29</sup> This is also true of the inhalation of oxygen in patients with cerebral arteriosclerotic disease in which the brain may be assumed to suffer from pre-existing ischemic cellular anoxia. In both groups of patients inhalation of high oxygen atmospheres, such as is provided by residence in a tent or oxygen room, may be followed by depression, crying spells, drowsiness, sleep, coma or delirium.

In a case of pulmonary emphysema, with moderately severe arterial anoxemia, inhalation of oxygen resulted in relief of dyspnea and cyanosis, and also in relapse into a comatose state which lasted six days. At the end of this period the patient awoke cheerful, rational and alert. Before treatment he had been apprehensive and depressed for several years, following oxygen treatment he was optimistic and unworried as long as the oxygen concentration in the atmosphere was not reduced. In a woman with cerebral arteriosclerotic disease, an irrational state began within five hours after inhalation of 50 per cent oxygen. Active delirium was once observed in a man with chronic anoxia due to pulmonary emphysema after he had been in an oxygen tent for a period of one hour. His arterial oxygen saturation had been 57 per cent prior to treatment.

In patients with chronic anoxia, the personality of the individual

organisms such as *Trichomonas vaginalis*, *Monilia albicans* and some others and thus prepare a means by which streptococci gain access to deeper tissue and institute a more extensive involvement than is usually observed in cases of parasitic vaginitis. It is not known that the foregoing parasites of the vagina have invasive properties in themselves but it is believed that they act in symbiosis with pathogenic bacteria and allow of deeper chronic involvement.

Defensive processes against infection in the cervix are manifested by an intricate anatomic structure of the endocervix and by the outflow of alkaline mucus, which is then liquefied and acidified in the vaginal vault by the action of the vaginal fluids. A mild chemical reaction thus occurs about the portio vaginalis. This process varies in different individuals and is influenced by their degree of natural immunity and general condition of bodily health. It is further varied by the hormonal influence on the vaginal epithelium in the quantity of glycogen available for conversion into lactic acid in the vagina, by the outflow of menstrual fluids and no doubt by other influences such as psychic stimuli not well understood.

Examination of the patient in anticipation of treatment for any condition is benefited by a general systemic review. A good physical examination is as essential in dealing with pelvic conditions as in dealing with conditions in any other portion of the body. Leukorrhea being the most frequent symptom of cervicitis, the nature of the discharge should be sought and its origin ascertained. Cultures and smears are advisable to determine the presence of *Neisseria gonorrhoeae*, *Trichomonas vaginalis* or *Monilia albicans* and the character of the pus and of the desquamated epithelial cells. There are likely to be a suggestive odor and consistency to secretions associated with the foregoing types of infection and gonorrheal infection is likely to reveal involvement of Bartholin's and Skene's glands. Malignant processes have an odor of necrotic tissue and secretions may be watery and blood stained.

Palpation should acquaint the examiner with the tone of the tissues of the vagina and supportive ligaments and the position, size and consistency of the cervix, the fundus and the adnexae. Nabothian cysts may possibly be more readily palpated than visualized. Palpation through the rectum is advisable if possible, as the adjacent cervical tissues and uterosacral and broad ligaments are often more accurately palpable by rectal than by vaginal examination.

Inspection of the cervix requires that the patient be in a comfortable position. If the vagina is unduly sensitive, a mild local anesthetic may be used. A good light is essential. Evidences of lacerations, edema, polyps, erosions, cysts, bleeding points and ulcerations are looked for. A small cold light introduced into the cervical canal may reveal by translucence deeply buried cysts which would otherwise be unsuspected. Gently pressing on the surface of the portio vaginalis with a blunt tipped probe may reveal irregularities of resistance and spongy

SPECULATIONS CONCERNING THE EFFECTS OF LOCAL ANOXIA IN  
CEREBRAL ARTERIOSCLEROSIS AND IN THE AGING PROCESS

Further investigation is urgently needed to determine the effects on the psyche and on brain metabolism of inhalation of high oxygen atmospheres in patients with cerebral arteriosclerotic disease in whom an ischemic anoxia may be present. In coronary sclerosis the administration of pure oxygen is followed in the vast majority of instances by prompt disappearance of anginal pain. Under these circumstances, the inhalation of 100 per cent oxygen may result in the oxidation of products of metabolism in the area of the heart muscle distal to the constricted artery. By analogy the possibility presents itself that acid products of incomplete oxidation may also be present in brain cells which have been exposed to a lowered oxygen supply because of arteriosclerotic disease. The inhalation of a high oxygen atmosphere may then be followed by changes in the chemistry of the brain. Analysis of internal jugular vein blood for lactic and pyruvic acid before and after oxygen treatment might reveal interesting changes in cases in which pre-existing brain anoxemia was present. The profound alteration in mental functioning which follows inhalation of a high oxygen atmosphere in these cases may be mirrored by alterations in the chemistry of the brain, concerning which at this time we have no data whatsoever. Himwich and I hope to be able to carry on studies of this kind. By exposing patients with senile changes to a very gradual increase in the oxygen concentration of the inhaled atmosphere, irrational manifestations may be avoided. The personality of these cases will be studied after acclimatization to an increased tissue oxygen tension.

Barcroft<sup>32</sup> suggested that the organism in gaining constancy of temperature, hydrogen ion concentration, water, sugar and oxygen, ultimately reached a stage of development at which man's higher faculties could develop. We may also refer to Claude Bernard's statement that the fixity of the internal environment is the condition of a free life. When biochemical alterations in the body are produced either by varying the tension of oxygen above or below that to which the individual has become adapted, serious alteration in mental functioning has been shown to result. It has also been shown by Pavlov,<sup>33</sup> Cannon<sup>34, 35</sup> and others that emotional reactions initiate changes in the organic state of the organism. The relation between psychic and somatic processes with respect to the effect of variable oxygen tension in the organism seems a fruitful field for psychosomatic investigation.

## ORGAN SENSITIVITY TO ANOXIA

Impairment of the inhibitory impulse is to my mind the outstanding sign of alteration in oxygen tension in the human organism, both in normal and psychoneurotic subjects exposed to low oxygen atmos-

ported<sup>2, 3</sup> from such situations as the bronchus, gallbladder, stomach, pharynx, prostate and anus and over the exposed surface of a long-standing chronic inversion of the uterus.

When the process of metaplasia occurs on the portio vaginalis of the cervix, the basal cells of the mucosa, which form the reproductive or functioning layer, seem to alter their product from the supposedly natural protective squamous type of epithelium to a more secretory glandular-like columnar epithelium and a so-called erosion is produced. The basal cells of both the columnar and the squamous types of tissues of the portio vaginalis are said to appear to be similar histologically.

If such a process does occur and produce an erosion as a result of cellular adaptation to unfavorable environment, could not a hypothesis go further and assume that cellular adaptation to unfavorable environment of frequent recurrence might proceed to the production of the disorderly groups of cell arrangement found in "carcinoma in situ" or "noninvasive epithelioma"? If those tumors are truly malignant tissue, and evidence<sup>4, 8</sup> seems to be accumulating that they may develop into the more common examples of malignant process, they offer an earlier step in diagnosis than the commonly accepted stage 1 carcinomas of the cervix. Carcinoma in situ is not diagnosed except by the pathologist and no doubt many such carcinomas have been destroyed by cervical cautery when a specimen for biopsy was not obtained. Some reports indicate reduction in frequency of primary carcinoma of the cervix since cauterization has become more prevalent.

Treatment of chronic cervicitis is aimed at eradication of the lesion. Actual destruction by some form of heat such as electric hot wire cautery is more commonly employed than surgical removal at the present time.

*Cauterization by nasal tip cautery* is a convenient process and is performed under direct visualization. It may be an office procedure and the patient may remain ambulatory. Other processes of actual destruction of diseased tissue may be equally efficacious and may be preferred by some but actual cautery has the advantage of simplicity of equipment, of visual control of extent and of minimal complications. Burning should be done slowly with a dull red, rather than a bright yellow, wire loop and should extend to a depth just through the mucosa. The lines should be spaced closely enough together so that radiant heat coagulates the intervening tissue and turns it ash-white. Cysts are evacuated by cautery puncture and their lining membrane is coagulated. If severed small vessels tend to spurt or ooze, they are nearly always controlled with the cautery by holding the glowing tip against the bleeding point. Sometimes the bleeding is effectually stopped by cauterizing deeper in an adjacent line, thus reaching the vessel in deeper tissue. When the cervix is considerably thickened and the lips are everted and contain deeply buried cysts, the cautery incisions may



lactic acid, pyruvic acid, since it has been shown that brain anoxia is the result of narcosis with these drugs (Himwich<sup>37</sup>) Although anoxic impairment of cortical function is followed by a lessened critical attitude in the individual toward himself and, when produced by a narcotic drug, is at times of striking therapeutic value, the immediate effect of anoxia on brain metabolism is impairment in emotional control and consequent disturbance in judgment

We are faced, therefore, with this interesting proposition, namely, that acute anoxia is followed by a form of emotional release that prevents the individual from employing his mature reason, judgment, memory and emotional control, but, on the other hand, the individual has manifested a need for freedom from the inhibitory critical faculty at certain periods in his existence This temporary freedom from the criticizing agency within himself is sometimes accomplished by man through the use of alcoholic beverages In addition, narcotic drugs which depress oxidative processes in the brain have been employed for more lasting results in the relief of anxiety and hysteria which have come on as the result of strain and shock of modern war, and civil life as well It must be borne in mind, however, that this narcosis is employed for a limited period of time in the treatment of psychoneurotic anxiety-depressive states, and that it does not permanently free the individual from the critical, inhibitory impulse within himself

#### COMMENT

The change in emotional behavior manifested by normal individuals as the result of a low oxygen tension in the atmosphere appears to be a most significant effect of anoxia This alteration in behavior is apparently due to diminished activity of the inhibitory impulse, manifesting itself in some instances by unreasonable euphoria, overconfidence, boisterousness and pleasurable excitement and in other cases by irritability and combativeness In a smaller group, drowsiness and lethargy take place at the start of exposure to a lowered oxygen tension Diminution of effective emotional control seems to be the decisive factor in impairment of judgment The emotional state created by anoxia is characterized in most individuals by a lessening of self-criticism The source of feelings of elation and exaggerated self-confidence may be traced to this diminished activity of the critical function

There is good similarity between the consequences of this form of anoxia and the effects of ingestion of alcohol The essential means by which alcohol exerts its action appears to be through the medium of suppressed oxidation in the brain Acute alcoholism has been classified as histotoxic anoxia The differences in manifestation of the effects of altitude anoxia and alcohol have been explained as due to variations in the environment at the time of exposure to anoxia and to the differ-

## SUMMARY

A chronically diseased cervix may be the source of either local or more systemic symptoms. The causation of cervical erosions is an interesting field of speculation. The suggestion is offered that these erosions may perhaps be a manifestation of metaplasia resulting from cellular adaptation to unfavorable environment and that so-called carcinoma in situ may be a further step in such a metaplasia. The foregoing is only suggested as a speculation, for proof of such process seems lacking at the present time. However, erosions and other cervical lesions justify the taking of a specimen for pathologic analysis and the correction of lesions of chronic cervicitis seems to have assisted in a reduction of the occurrence of cervical malignant disease.

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which the individual has become accustomed would seem to be a promising field for future investigation

### SUMMARY

Impairment in emotional control appears to be the most significant response to anoxia. In some individuals exposed to low oxygen atmospheres, overconfidence, elation, euphoria, exaggerated self-esteem and boisterousness are the outstanding manifestations of decreased activity of the inhibitory impulse. This is accompanied by impairment in reason, judgment and memory. In other cases, dullness, drowsiness, irritability and lethargy are the consequences of exposure to a low oxygen tension in the atmosphere. Impairment in emotional control may manifest itself by lack of capacity to inhibit the sexual or the aggressive impulse. The environment in which anoxia is experienced and the personality of the individual himself are factors which determine the type of alteration in emotional behavior produced by anoxia. The effects of anoxia, as induced by a decreased tension of oxygen in the atmosphere, are very similar to those resulting from ingestion of alcohol.

The inhalation of oxygen-enriched atmospheres by individuals who have had pre-existing chronic anoxemia results in a profound disturbance in mental function, with impairment of emotional control, reason, judgment and memory, and at times with irrationality and coma. The irrational or comatose states induced by inhalation of high oxygen atmospheres are temporary and subside during the continuation of oxygen treatment. This type of disturbance in mental functioning takes place in patients with chronic pulmonary disease accompanied by arterial anoxia and in patients with cerebral arteriosclerotic disease in whom anoxia is the result of constricted arterial blood supply. In patients with known pre-existing chronic anoxia, either due to pulmonary or cerebral disease, the oxygen concentration in the atmosphere should be increased slowly and gradually, to avoid the consequences of abrupt change in oxygen pressure in the brain. Since the brain is the organ most sensitive to anoxia, both in terms of function and pathological change, investigation of the effect of restoration of an increased oxygen pressure in patients with cerebral arteriosclerotic anoxia offers an opportunity for investigation of the aging process.

The capacity to inhibit impulse, i.e., to control one's emotions, has been shown to be acutely dependent on the maintenance of an accustomed oxygen tension in the brain. Altering the oxygen pressure in the atmosphere below or above that to which man has become adapted may be followed by a characteristic profound disturbance in mental functioning. The individual may adjust himself to low oxygen pressures through acclimatization, similarly, the patient with chronic anoxia may be gradually acclimatized to a normal oxygen pressure.

## URETHRITIS

One of the most common maladies of the female is inflammation of the urethra. This lesion frequently is found in women more than forty years of age. The classic experiment of Winsbury White did much to explain the frequent association of urethritis and trigonitis with endocervicitis, and also the fact that urethritis frequently accompanies monilial, trichomonal, gonorrheal, puerperal and postabortive infections. White demonstrated the relation between the cervix of the uterus in guinea pigs and the trigone of the bladder. He injected India ink into the cervix uteri and later found the dye in the lymph spaces where the bladder and vagina are in intimate contact.

The most common symptoms of urethritis are frequency and burning on urination. Urgency and dysuria also may be present. In the more severe cases tenesmus is noted. These irritative phenomena usually are aggravated during micturition and many times reach their greatest severity immediately after the act is completed. Hematuria is not common but may be present. If symptoms of external irritation are present, they usually are caused by associated meatitis. Dyspareunia occasionally is encountered, particularly if there is an associated urethral diverticulum. Any or all of these symptoms may be present in the various types of urethral inflammation.

The remainder of the discussion of urethritis deals with two forms of this condition; namely, simple urethritis and senile urethritis.

**Simple Urethritis.**—This form of urethritis, which is by far the more common, can be divided into granular and cicatricial types with or without associated inflammatory tags. On urethroscopic examination of the granular type the mucosa is raised, reddened and has a granular appearance in scattered regions or throughout the whole urethra. Purulent secretion seldom is encountered. Frequently there is diffuse tightness of varying degree to the passage of the instrument along the canal. This may exist alone or in association with the granular change. At times a cicatricial process may have advanced to such a degree that there is a true stricture with symptoms of obstruction to the passage of urine as well as the objective findings of residual urine and trabeculation of the bladder.

In many cases of granular and cicatricial urethritis there are localized regions of mucosal proliferation, particularly at the vesical neck, which are referred to as inflammatory tags. These swollen reddened regions in themselves cause no particular difficulty and are only another manifestation of the granular change in the mucosa.

In the treatment of simple urethritis, the use of irritating medicines, frequent instrumentation and all forms of cautery should be kept at a minimum. In the granular type, the use of a mild astringent such as argyrol, 5 per cent, or protargol, 1 per cent, applied once daily for a week on an applicator of cotton and left in place for five to ten minutes usually is of benefit. Warm sitz baths also should be taken daily.

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## URETHRAL DIVERTICULUM

Many causes have been recorded as being responsible for urethral diverticulum. This condition probably is acquired and may arise from infected periurethral glands. The symptoms are much the same as those encountered in cases of simple urethritis but frequently are more severe. Occasionally, swelling may be palpated in the anterior vaginal wall which on pressure produces a discharge from the urethral orifice. Pain on walking and dyspareunia occasionally are noted.

The diagnosis is made by demonstration of the pocket with an opaque medium. On cystoscopic examination one or more minute scarred openings may be seen in the floor of the urethra. If possible, a soft 4 F. ureteral catheter is passed into the opening and coiled in the pocket. Opaque medium then is injected and a roentgenogram made. At times a mass in the anterior vaginal wall may be palpated. The urethral diverticulum occasionally may contain calcareous material.

The treatment is surgical. Local therapy in the form of strong astringent solutions or fulguration are only rarely of value. Surgical excision of the pocket through a vaginal approach, with careful closure of the urethral opening and repair of the urethral floor usually are necessary to relieve this distressing complaint.

immediate cause of death, and hence are not carefully studied by the pathologist

Only a few decades ago pathologists ignored the coronary arteries and the smaller vessels in the myocardium proper because the medical world, outstandingly Osler, McKenzie and Neusser, were unaware of the importance of coronary artery disease with coronary thrombosis as a direct cause of death. The pathologist considered duodenal ulcer an infrequent finding since careful postmortem inspection of the duodenum was long ignored as being of less significance than the stomach. We now know that the frequency of duodenal ulcer far exceeds that of gastric ulcer. Gallstones, unless some complications set in, likewise are not a direct cause of death. When a patient died of some intercurrent disease and gallstones were found by the pathologist, he looked upon cholelithiasis as having been asymptomatic and described such patients as gallstone carriers and not gallstone sufferers. We now know that reflex gastro-intestinal and even extragastric symptoms, such as cardiospasm and angina pectoris,<sup>2</sup> are caused by gallstones, and that almost every gallstone carrier is a gallstone sufferer.

Since the span of life has been extended to the period when arteriosclerotic changes in the blood vessels usually take place, the syndrome of arteriosclerotic vascular disease of the digestive tract is of practical importance. We therefore hope to awaken interest in this subject in the clinician and pathologist. This discussion will deal primarily with the diseases of the arteries, and will concern itself, as indicated by the title, chiefly with arteriosclerotic changes in the arteries of the digestive organs.

Each organ, in order to function properly, depends on its blood supply. An organ or muscle at work requires seven times the amount of blood needed during rest, and this amount of blood can easily be supplied, as was demonstrated by Barcroft<sup>3</sup>. He showed that the blood reservoir in the liver, spleen, lungs and skin is so vast that it supplies the necessary amount of blood not only during work, but even during shock or other emergency. If the vascular system is defective the organs supplied by impaired blood vessels must necessarily suffer the consequences of interference with their proper nutrition.

#### THE CAUSES OF ARTERIOSCLEROSIS

The most important disease of the larger and small vessels interfering with the blood supply is arteriosclerosis. From our clinical observations, the immediate cause of arteriosclerosis is undoubtedly *senescence*, a degenerative process that life brings with it. The objection that in some countries, such as China (Snapper<sup>4</sup>), there is little or no arteriosclerosis does not vitiate this concept. The causes leading to such degeneration are numerous, explaining why it occurs earlier

small blade or nail file the amount which is to be snuffed or blown into the nares.

Some patients who are "supposed" to have diabetes insipidus, in reality, are only nervous water drinkers. For one reason or another their habit of drinking large quantities of water or other fluids has developed. Only occasionally do they drink as much as the patient who has diabetes insipidus and practically never do they drink as much during the night. A patient who has diabetes insipidus may drink as much or more during the night as during the day. Such a patient may arise eight or ten times during the night to urinate and drink; the nervous water drinker rarely presents this history. The concentration test,<sup>4</sup> easily performed, determines the diagnosis since the nervous patient concentrates urine normally, but the patient who has untreated diabetes insipidus cannot concentrate urine to above a specific gravity of more than 1.010.

#### THE ANTERIOR LOBE OF THE PITUITARY

This small gland has only two types of secreting cells, the acidophil cells and the basophil cells. There is no known secretion from the chromophobe cells. Physicians are asked to believe that these two types of cells are capable of secreting a large number of distinct hormones, such as one or more gonadotropic hormones and hormones essential for growth, the function of all the other endocrine glands and the utilization of food and water. There is no question about the importance of this gland in the growth, maturation and function of the body; there is serious doubt as to whether this is accomplished through the production of so many distinct hormones. These matters have been summarized completely in another publication.<sup>2</sup>

Clinically, there are not many recognized disturbances of this gland. Underfunction, underdevelopment or removal prior to puberty produces the clinical picture of *dwarfism* or *infantilism*; underfunction or removal after puberty results in the syndrome of *hypopituitarism*. There are, of course, many variations but the condition which follows the surgical removal of the gland is well known to all physicians. Some have seen one of the rare cases of *Simmonds'* or *Sheehan's syndrome* which follows the destruction of the anterior pituitary gland. These occur most often in women who have had a severe hemorrhage or shock after childbirth. All have seen the clinical picture which follows the destruction of the pituitary due to adenoma of the chromophobe cells. These typical examples are mentioned because often the diagnosis of pituitary insufficiency is made on insufficient data. Many fat boys have the clinical picture known as *Fröblich's syndrome* but few have any organic disease of the pituitary; most patients whose condition is diagnosed as Simmonds' disease are really suffering from anorexia nervosa and certainly few undersized individuals are suffering from pituitary insufficiency.



of dizzy spells out of proportion to the length of time the patient stands, and fainting when on a long march or after standing for a prolonged period due to irritable carotid sinus reflex. Even transient increase in blood pressure in such individuals eventually must lead to disturbance in the layers of the blood vessels proper—intima and media—permanently damaging these arteries. Whether such an individual can be trained as a useful member of the armed forces is problematic. Each case must be under prolonged medical and psychiatric observation before a decision can be made.

The state during which the functional changes alone predominate, Walko<sup>11</sup> called *angioneurotic*. When pathologic changes develop, the state is that of *angiosclerosis*. The angioneurotic state is reversible, although leading to symptoms which are unpleasant and sometimes alarming. During the stage of true arteriosclerotic changes the process is irreversible with persisting, more alarming symptoms leading in many instances to fatal termination. There is marked epigastric pulsation, but no pulsation can be detected in the suprasternal notch because of narrowing of the thoracic aorta.

In the hypoplastic type the functional overwork of the blood vessels causes spasticity and the resulting digestive symptoms are due to local ischemia. The sensitivity of the capillaries in the stomach can produce transient changes in the gastric mucosa and even ulcer formation, as was demonstrated by the brilliant work of Wolf and Wolff.<sup>12</sup> Upon the same fact, the spasmogenic theory of von Bergmann as a causative factor of ulcer is based.

2 The Plethoric Type—In contradistinction to the underdeveloped type, there is a second type in whom angiosclerotic changes can occur without being preceded by angioneurosis, that of the *status apoplecticus*. Although the arteriosclerosis in these individuals is most often generalized, it is more outspoken and sometimes predominantly present only in the splanchnic vessels, especially if such an individual is afflicted with *plethora abdominalis*. In the latter condition, which is most often encountered in very obese individuals who lead a sedentary life, the functional abuse of the blood vessels is caused by their overfilling, resulting in congestion of the organs supplied. This leads at first to passive hyperemia, later to active hyperemia and chronic changes in the organs proper. Enlargement of the liver, often of the heart and even of the spleen may be encountered. With the increase of local circulatory disturbances in the abdominal vessels, there is an increase in the resistance in the splanchnic system as well as an increased resistance in the smaller vessels and marked elevation in blood pressure.

In both the hypoplastic and plethoric types, the arteriosclerotic changes in the blood vessels are not of the same severity throughout the entire body. In the small arteries of the gastro-intestinal tract

it occurs in a girl prior to puberty, she will undergo premature maturity, may menstruate, develop large breasts, and so forth; if it affects a woman, amenorrhea and masculinizing changes follow. In both a peculiar obesity will involve the trunk with the Buffalo hump across the shoulders and the arms and legs are relatively thin. The skin is often plethoric and covered with acne and hair. Wide purplish striae are present. Examination shows variations of hypertension, osteoporosis, polycythemia, glycosuria, hyperglycemia and elevation of the basal metabolic rate. The picture is comparable in many respects to that produced by a tumor of the adrenal cortex or an arrhenoblastoma of the ovary. Once these conditions have been excluded, the only treatment is roentgen therapy to the pituitary.

After such treatment, many months pass before any improvement may result and only too often the whole sad picture may recur after it has seemed to disappear completely. The seriousness of this condition is an important reason for careful application of the term; records are available of patients who have committed suicide after receiving this diagnosis.

#### THE THYROID

Only a small fraction of the thyroid extract which is manufactured commercially is used for the treatment of *myxedema*; most of it is used for conditions which are "supposed" to be associated with a lack of this hormone. Myxedema responds excellently to administration of thyroid extracts. Because myxedema is a clear-cut entity caused by the lack of a single hormone, the administration of a small amount of thyroid extract completely controls the condition. I have not seen any patient with myxedema who required more than 2 grains (0.13 gm.) of desiccated thyroid extract per day and the addition or subtraction of even  $\frac{1}{4}$  grain (0.016 gm.) is reflected in the patient's condition and basal metabolic rate. I have never seen a patient with uncomplicated myxedema who could not tolerate the use of thyroid extract, although many of these patients have unpleasant symptoms, such as generalized aches and pains, for the first few weeks of treatment. Very rarely thyroid extract cannot be administered because of the coexistence of a serious condition, such as severe angina pectoris.

Contrast this with all the patients with "supposed" thyroid deficiency. One such patient has a low basal metabolic rate ( $-16$  per cent) and she complains of being chronically tired. "I feel low all the time," she states. Her basal metabolic rate is not all that is low; so may be her hemoglobin, blood count, blood pressure and gastric acids. Many organs may be low including a "dropped stomach," "dropped colon," "dropped kidneys" and a retroverted uterus. Yet the treatment that is most likely to be tried first is administration of thyroid extract. After she has taken 5 grains (0.3 gm.) daily for five weeks her basal metabolic rate is found to have risen only to  $-14$  per cent.

intima and later spread to the media. The changes in the smaller vessels may be generalized, but in a large number of cases they are confined to one or the other organ. This explains why in some cases the symptoms are more outspoken in some organs than in others.

Frequently small scars due to *infarcts*, particularly during advanced and sometimes in middle age, are accidental findings in the kidneys and spleen at postmortem examination. Neusser<sup>15</sup> used to remark that many cases of pain in the left hypochondrium, in the lumbar region, or in one or the other loin, all unexplained during life, may have been the result of small infarcts due to local vascular disease of these organs.

Dock<sup>16</sup> recognizes several forms of arterial degeneration, some purely aging processes, others of more complex and obscure origin. The normal aging process he terms *fibrosis with ectasia* and considers the loss of elastic and muscular elements in the media analogous to the skin changes which cause wrinkling or to changes in the cartilages which make them susceptible to calcification and fibrillary degeneration in adult life. It leads to elongation, widening and tortuosity of the temporals, often seen very early in life—before the age of thirty—and which can be observed fluoroscopically in the aorta. The arteries, being less elastic, raise systolic blood pressure. But the widening compensates in some degree by creating a big reservoir of low elasticity to replace the small and highly elastic reservoir that is present in youth. According to Dock, such change in the coronaries makes occlusion less likely.

The above mentioned *Monckeberg calcification* is also due to aging and rarely leads to any break or blockade of the vessels. On the other hand, the medial mucinous degeneration predisposes to rupture or dissection of the aortic wall. The *atheromatous lesions* are spots, focal lesions scattered in the vascular bed, more numerous in the lower abdominal part of the aorta and in the iliac arteries, also common in the coronary arteries and in the arteries of the legs. The hypertensive individual has more and larger atheromas than those with normal blood pressure. Individuals with congenital hypercholesterolemia have such atheromatous changes early in life which may cause death due to coronary thrombosis in the 'teens or early twenties.

#### PATHOGENESIS OF HYPERTENSION

**Cholesterol Metabolism and Hypertension**—Anitschkow,<sup>17</sup> by his experimental work, was the first to associate the excessive intake of fat resulting in the deposition of lipids, particularly cholesterol, in the blood vessels, with changes eventually leading to arteriosclerosis. Aschoff carefully studied the pathological relationship of cholesterol metabolism to arteriosclerosis. (References to these important experiments are found in the classic on the subject by Cowdry<sup>17</sup>) Import-

If calcium lactate is used, it should be stirred in boiling water until a clear solution results, since it is poorly absorbed if it is not in solution. Calcium tablets are much less effective. Vitamin D can be given by mouth twice daily.

Two other substances which should be mentioned are calciferol (vitamin D<sub>2</sub>) and dihydrotachysterol (A.T. 10). These are crystalline products obtained by the irradiation of ergosterol. They are effective when given by mouth and are extremely potent. As in the use of the parathyroid hormone, care should be exercised to avoid overdosage.

### THE PANCREAS

The chief endocrine function of the pancreas is, of course, the production of insulin. The role of its other endocrine and excretory products will not be discussed in this paper. *Diabetes mellitus* usually is recognized easily and the treatment with diet and some type of insulin is well understood. The only condition which may be confused with diabetes mellitus which I will mention is that of the patient whose urine shows some reducing substance and whose blood sugar is normal. If a sugar tolerance test is performed and the result indicates decreased tolerance for sugar, then the diagnosis of diabetes mellitus appears on the patient's record. From that moment on it will be difficult, and sometimes impossible, for the patient to obtain life insurance; if insurance is issued, it is with increased premiums. One such patient returned to the Clinic and the results of repeated sugar tolerance tests were normal. Life insurance finally was granted. The sugar tolerance test is not a specific test for the presence or absence of diabetes. It is affected by absorption, by obesity, by the patient's diet, by many disturbances of the liver and muscles and by the various endocrine glands. Even when the test on a thin person who has been on a high carbohydrate regimen is positive the interpretation may be questioned. In cases of the type under consideration in which the level of the blood sugar is normal, the patient can be as well protected by discussing the need for further observation as by doing a sugar tolerance test. This test is of much more importance when it gives a negative result than when the result is positive. When the result is questionably positive the diagnosis should be deferred.

In contrast to definite diabetes mellitus is *hyperinsulinism*. The first proved instance of this disease was reported in 1927<sup>1</sup> and the total number of proved cases is probably less than 200, yet the literature contains reference to thousands of supposed cases. A patient who has proved hyperinsulinism usually has clear-cut symptoms of a severe insulin reaction occurring only when he is fasting or has been exercising. His blood sugar readings at such times are very low. He obtains prompt relief from the administration of carbohydrate and all symptoms disappear completely after the successful removal of an insulin producing adenoma of the pancreas. Unfortunately, the term<sup>7</sup> "hyper-

**Angiotonin**—According to Page,<sup>24</sup> reduction in pulse pressure and possibly temporary drop in blood flow may set the renal vasomotor system into action. An enzyme called rennin, which is present in the renal tubular cells, is liberated into the blood stream. It acts on the alpha globulin of the plasma to form a substance known as angiotonin. The globulin has its origin in the liver. Angiotonin is the substance which raises the blood pressure. It increases the force of the heart beat, as shown in the experimental animal and in the enlargement of the heart seen at the bedside. Although the peripheral vessels of the skin are likewise constricted, there is no reduction in the blood flow, so that the skin is not necessarily pale. In the kidneys there seems to be constriction of the small arterioles distal to the glomeruli which results in increased pressure within the glomerulus and reduction of blood flow around the tubules. This fascinating work, as well as that of Goldblatt, although of great importance, still leaves many loopholes as to the causes of increased blood pressure without any renal changes.

**Instability of the Vasomotor System and Its Influence on Peripheral Resistance**—These factors significantly affect the blood pressure. Marked spasm in the arterioles and small arteries occurs in certain types of individuals with a sensitive, unstable vasomotor system. If the vasomotor instability affects the vascular system, spasm of the peripheral vessels of the skin or the legs may give rise to the well known syndrome of extreme pallor and numbness, and even thrombotic changes like endarteritis of the temporal arteries or of the pulmonary vessels may take place. But in all such instances increase of the blood pressure need not necessarily coexist. However, if such spasm takes place in the splanchnic system an increase in blood pressure results. During the state of angioneurosis the spasm can be transient and reversible, as mentioned above, but it can become persistent and lead to actual angiosclerosis. If that persistent angiospasm is confined to the kidneys it may lead to serious hypertension of the essential type, eventually of the malignant type.

#### SYMPTOMS DUE TO ARTERIOSCLEROTIC CHANGES

**In the Hypoplastic Type**—In this type, in whom vasomotor instability is a causative factor, the gastro-intestinal symptoms may be marked even during the angioneurotic stage. The symptoms, however, are vague and transient in nature, not characteristic enough to establish a diagnosis. The usual complaints are *fullness* in the epigastrium soon after meals, *nausea*, *capricious appetite*, and at times *aversion to food* for weeks leading to considerable emaciation. The blood pressure may reach 140 and even 160 systolic, sometimes rise as high as 180 systolic, due to nervous instability. The blood pressure usually drops 20 or 30 mm and more of mercury as the patient calms down.

and other objective findings, both laboratory and clinical, such as more normal sex response, lowering of the voice, improvement in genital development, condition of the skin, hair and so forth. To repeat, I question only the incidence of the male menopause.

#### THE ADRENAL MEDULLA

There is no known syndrome associated with the underfunction of the adrenal medulla.

Paroxysmal hypertension is usually due to an adrenal medullary tumor, a *pheochromocytoma*. This is the rarest of all tumors of the endocrine glands. The usual history is one of sudden, marked rises of the blood pressure with severe vasomotor symptoms due to the paroxysmal outpouring of large amounts of adrenin from the tumor. Roth and Kvale<sup>10</sup> have described the use of histamine to establish the diagnosis. A single injection of a small amount of histamine produces a typical attack. The treatment is, of course, the surgical removal of the tumor; during the operation care must be exercised not to produce another attack. To do this manipulation of the tumor must be avoided until the vessels are clamped.

#### THE ADRENAL CORTEX

*Addison's disease* is, of course, the result of destruction of the adrenal cortex from tuberculosis or of simple atrophy. All physicians have seen cases of Addison's disease and recognize the pigmentary changes (not always present), the loss of weight and strength, the lowering of the level of sodium, chlorides and sugar and the elevation of potassium and urea in the blood, and the signs and symptoms of acute adrenal failure. Treatment consists in substitutional therapy, replacing the necessary electrolyte constituents and administering available hormones. Theoretically, the ideal treatment should be the administration of a whole adrenal cortical extract. The chief obstacles in this treatment are, first, the expense and, second, the fact that the extracts are not as potent as seem desirable. The time may come when a more potent, less expensive extract will be available. The extract from the adrenal glands of hogs may prove more active since this extract contains more of the "blood sugar raising" principle than do present commercial products. The only synthetic hormone of the adrenal cortex which has had extensive clinical use is desoxycorticosterone acetate<sup>12</sup> which can be administered hypodermically, by subcutaneous implantation of pellets, by the usual oral method or sublingually. This hormone is the most potent "salt and water retaining" hormone of the cortex but has no "blood sugar raising" effect. It has two disadvantages, first, the expense and, second, its incompleteness. If synthetic hormones are to be used, a mixture of desoxycorticosterone acetate with other fractions which will aid in other functions

to a great deal of pain, colicky in character, which appears periodically. The pain is confined mostly to the right of the abdomen. There is also a great deal of burning in the upper abdomen radiating to the lumbar region. Not infrequently, the pain is neuralgic in character, and the burning and tearing nature of the pain may persist day and night, it may come on at any time and last from ten to fifteen minutes, and sometimes continue for an hour or two. Where the pain occurs one or two hours after meals, gastric or duodenal ulcer is suspected. In these conditions food which causes fermentation in the stomach aggravates the pain.

At times sclerosis causing narrowing of the abdominal aorta and its branches gives rise to *diffuse generalized abdominal pain and pulsations* throughout the entire abdomen. A loud blowing systolic murmur is heard in these cases over all the vessels of the abdomen. The vessels can be palpated, feel cordlike, and are tender to pressure. Meteorism is quite marked and according to Adolph Schmidt and his pupil, Kato, it is due to the failure of the intestinal tract to absorb the gases. The symptoms are usually attributed to some other gastro-intestinal disease. The intake of food is cut down to a minimum by the patient because of distress after eating, thus resulting in considerable emaciation and secondary anemia which arouse suspicions of malignancy, strengthened by the fact that the individual affected is usually of advanced age, with a low or no gastric acidity. It is a well known clinical fact that as long as the arteriosclerotic symptoms are not confined to the digestive organs, the patient does not as a rule lose weight and usually appears perfectly healthy, in other words, if cerebral or thoracic symptoms predominate the patient's state of nutrition does not suffer.

#### SCLEROSIS OF THE GASTRIC AND INTESTINAL VESSELS

If the sclerotic changes are most marked in the vessels of the gastric mucosa, localized trophic changes result causing distressing gastric symptoms. In these cases there is *persistent pressure and pain in the upper abdomen independent of meals but aggravated by food*. Nausea and loss of appetite are very marked and may lead to loss of weight. In cases of aneurysmal formation with subsequent rupture, severe uncontrollable gastric hemorrhages may occur. This is, however, rare. Rupture of arteriosclerotic vessels in the intestines causing intestinal hemorrhage is more common. According to G. Singer,<sup>25</sup> intestinal hemorrhage due to intestinal atherosclerosis is characterized by the fact that it recurs very frequently and that the patients recuperate very rapidly. This is an important differential diagnostic sign from gastro-intestinal bleeding due to cancer, varices from the esophagus or rhages caused by thrombophlebitis in the splenic and hepatic vessels.

fibrosa disseminata, etc.) are 'spotty'; but hormones do not affect one arm and not the other!

"5. End-organ unresponsiveness does not mean abnormal glands (American Indians do not raise beards).

"6. Obesity is not 'typed' according to glands; it usually results from polyphagia and abulia and not endocrine dysfunction.

"7. Normal endocrine glands characterize most psychopathic (homosexual, etc.), psychoneurotic or psychotic persons.

"8. Obscure diseases usually are not made lucid by incriminating the endocrines."

### SUMMARY

The real disturbances are summarized in table 1.

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usually attributes the attacks to exertion, psychical trauma or heavy meals, especially such that cause abdominal distention. In some cases the pain may wake the patient from sleep. Some patients cannot lie flat on their backs and are compelled to sleep in a semirecumbent position. In most cases the abdomen is distended and meteorism is marked. The diaphragm is pushed up to such an extent that it causes dyspnea, palpitation and increased pulse rate.

*Meteorism* may be as marked as in peritonitis, but unlike the latter, intestinal sounds can be detected on auscultation. When borborygmus sets in, the patient usually is relieved. Vomiting occurs but it is not the rule. The meteorism usually affects the cecum and transverse colon. In the case reported by Jacob Meyer the distention of the transverse colon was so marked as to fill the entire abdomen. In some of the cases it is associated with thrombo-angitis obliterans. Jacob Meyer speaks of the condition as thrombo-angitis obliterans of the abdominal vessels. His case and the one reported by G. A. Friedman were associated with thrombo-angitis obliterans of the lower extremities. We saw two cases associated with thrombo-angitis obliterans, in one of which both legs had to be amputated.

**Diagnosis**—The diagnosis of dyspragia intestinalis is very difficult because a number of other intra-abdominal conditions may give rise to similar symptoms as, for instance, cholecystitis, appendicitis, nephrolithiasis, intestinal obstruction, hemorrhagic pancreatitis, twisted ovarian cyst, lead colic, tabetic crises, or nicotine abuse. In the presence of thrombo-angitis obliterans of the lower extremities or general arteriosclerosis, the diagnosis may be possible. The diagnosis is also facilitated if there is considerable freedom of symptoms between one attack and the other.

**Prognosis**—The prognosis in these cases depends on whether the symptoms are angioneurotic or angiosclerotic in nature. If the symptoms are due to angioneurosis, the patient may, after repeated attacks, become free from symptoms and remain so for the rest of his life. In the angiosclerotic stage there is a tendency for the symptoms to recur and become more marked, sometimes simulating malignancy because of marked anemia and emaciation.

#### THROMBOSIS OF THE MESENTERIC VESSELS

The distribution of the mesenteric vessels to the abdominal organ is as follows: the superior mesenteric artery supplies through the inferior pancreaticoduodenal artery, the duodenum, through the jejunal and ileac arteries, the jejunum and ileum, through the ileocolic artery, the lower ileum and cecum, through the right colic artery, the ascending colon, and through the middle colic artery, the right half of the transverse colon. The left colic artery supplies the sigmoid through the sigmoid artery. The upper rectum is supplied by the

entity not thus far encountered elsewhere. As judged by published case reports, hyperparathyroidism has remained a rare disease and generally is recognized only in the presence of extensive disease of bone.<sup>32</sup> By contrast, by 1942, Cope<sup>24</sup> and Albright were able to report a total of sixty-seven cases in which the presence of hyperparathyroidism was proved at operation, a series far larger than that observed by any other group of investigators. I am happy to acknowledge, therefore, that I have drawn freely from the observations and experience of Albright and his associates.

The first case of hyperparathyroidism observed at the Clinic was reported by Wilder<sup>46</sup> in 1929. For many years, the diagnosis was made very infrequently. Alexander, Kepler, Pemberton and Broders<sup>10</sup> in 1944 were able to collect only fourteen cases of proved hyperparathyroidism that had been observed at the Clinic in a period of fourteen years; namely, from January, 1929 to September, 1942. Considering the much greater incidence of the disease encountered by Albright and his associates at Boston, it appeared reasonable to assume that, at the Clinic as well as elsewhere, the presence of the disease was being overlooked. It seemed possible that the criteria which we had established for the diagnosis of this disease were unduly rigid. Early in 1943, a definite attempt was made to improve diagnostic accuracy by soliciting the co-operation of internists, urologists and surgeons.

In a period of approximately two and a half years, that is, from September, 1942 to January 31, 1945, inclusive, the presence of hyperparathyroidism was proved by operation in twenty-four cases. This is in marked contrast with the fourteen cases in which the presence of the disease was proved in the previous fourteen years. Our findings in the twenty-four cases fully confirm the observations of Albright and his associates. In seven, or 29 per cent, of the twenty-four cases, there was a clinical picture of classic osteitis fibrosa cystica. Minimal lesions of the skeleton were present in nine, or 38 per cent, of the cases but in eight, or 33 per cent, of the cases there was no evidence whatever of osseous lesions.

#### PRIMARY HYPERPARATHYROIDISM

Hyperparathyroidism is classified as secondary when it results from compensatory hyperplasia of the parathyroid glands due to some other disease such as nephritis or rickets. It is classified as primary when no such etiologic factor is present.

Primary hyperparathyroidism is nearly always caused by one or, occasionally, two adenomas of the parathyroid glands. The tumors which produce hyperparathyroidism are small and more often than not are impalpable. They may occur retrosternally and may be overlooked even when the neck is explored surgically. There are a number of instances in which two or even three operations have been necessary before the tumor could be located.

vessel is obliterated there is an increased excitability of the motor nerves and the muscles of the intestines leading to increased intestinal peristalsis which is responsible for the diarrhea. At times the increased excitability of the intestines causes spastic contraction of the colon with obstinate constipation. As a rule, however, there is diarrhea associated with severe pains and vomiting.

The *onset* is usually sudden whether the thrombosis affects the artery or the vein. The patient complains of severe *colicky pains* and *nausea*. *Violent peristaltic contractions* of the affected anemic part of the bowel are usually present. *Singultus* and *vomiting* are early symptoms. Vomiting is rarely fecal. Hematemesis is also very rare, but if present it is due to the blood regurgitated from the intestines into the stomach. *Bloody stool* is more frequent and according to most statistics it is encountered in 50 per cent of the cases. Another very striking symptom is *collapse*. The pulse is rapid, the temperature subnormal, the face is pinched, and the extremities are cold.

The first symptoms resemble greatly those of intestinal obstruction due to strangulation. However, in contradistinction to strangulation, thin, bloody, bright red or dark red stools are present in mesenteric thrombosis. The loss of blood may be considerable and in part responsible for the fatal termination. In a small number of cases death occurs during the stage of shock before the symptoms of intestinal occlusion set in. The initial symptoms of collapse last from about twelve to twenty-four hours after which the signs of intestinal occlusion make their appearance and they remain throughout the course of the disease. Very often the pains are so severe that the patient moans continuously. At times visible peristalsis may be noticed over that part of the colon which is obstructed. Death usually results within the first week. Very seldom recovery takes place. It may be stated that the longer the disease lasts and the milder the symptoms the better are the chances for the reestablishment of the collateral blood supply.

**CASE REPORT**—The patient, a man, thirty-five years of age, previously healthy, when seen by us complained of severe diffuse pain in the abdomen which was more acute on the left side and necessitated morphine for relief. (This patient was also seen by Dr. B. S. Oppenheimer who observed him throughout the entire course at the Mount Sinai Hospital, New York.) We differed with the suggested diagnosis of retroperitoneal sarcoma. Because of the very rapid growth of the tumor, the severity of pain and the fact that the tumor was fixed it seemed to us that the tumor was due to an enlarged spleen secondary to thrombosis of the splenic vein, although the splenic notch could not be felt. The patient was taken to the Mount Sinai Hospital and studied for some time. At exploratory examination a splenic vein thrombosis was found and the spleen was removed.

The patient made satisfactory progress for several days postoperatively, when he developed subphrenic suppuration and pyopneumothorax and died seven days after operation. The autopsy by Dr. Klemperer disclosed that in addition to the

in our experience the urine usually is found to have a low specific gravity.

Excessive excretion of calcium and phosphorus leads to the formation of renal stones in a high proportion of cases. In twenty, or 80 per cent, of twenty-four cases observed in the past two years, renal calculi were present. As one would expect, some of the stones were composed of calcium phosphate but, for reasons not understood, most of the stones contained calcium oxalate. The stones which occur in hyperparathyroidism may produce all the symptoms and complications common to renal calculi from any source.

In some cases, calcium is deposited in the renal substance, probably in the renal tubules. This results in nephrocalcinosis, a diffuse calcification of the renal parenchyma associated with sclerosis and destruction of renal substance which may progress to a stage where serious renal insufficiency occurs. The condition is generally regarded as irreversible even though the hyperparathyroidism is eliminated. Baker and Howard<sup>14</sup> have reported a case of hyperparathyroidism, nephrocalcinosis and renal insufficiency in which, after excision of a parathyroid tumor, a remarkable degree of recovery at first took place. Severe hypertension developed later and the patient died of a dissecting aneurysm.<sup>38</sup>

A serious degree of renal insufficiency can, of course, result from pyelonephritis or hydronephrosis caused by renal calculi. Pyelonephritis and nephrocalcinosis make damage to the kidney by far the most important consequence of hyperparathyroidism and are ample justification (if such be needed) for seeking means of improving diagnostic methods.<sup>8</sup>

*Symptoms Resulting from Involvement of the Skeleton.*—In many cases in which the absorption of calcium from the diet is approximately equal to that lost through the urine, no evident change occurs in the skeleton. In other cases, there may be any degree of skeletal involvement from minimal demineralization to the most profound depletion and disarrangement of the entire skeleton which are characteristic of advanced osteitis fibrosa cystica. Patients with minimal skeletal changes may have no symptoms whatever or, at the most, may have vague aching and pain.

In cases in which the disease is advanced, various tumors, cysts, pathologic fractures and deformities may occur and be accompanied by intense pain and discomfort. Favorite sites for such lesions are the long bones, ribs, pelvis, and the metacarpal and metatarsal bones. Brown tumors of the jaw, so-called epulis, are often but not invariably indicative of this disease. Loss of height, kyphosis and other deformities of the skeleton may be observed.

Pathologically, the osseous lesions show extensive resorption and decalcification of bone with much fibrous proliferation, but the most conspicuous feature is the intense cellular activity resulting from in-

In other cases, the intestinal symptoms predominate. The *pain* is colicky in nature, confined to the lower abdomen, accompanied by marked *abdominal distention* and obstinate *constipation*. The pain may localize itself in the ileocecal region giving rise to symptoms of appendicitis or in the sigmoid region simulating sigmoiditis. In either case the diagnosis is soon cleared by the presence of bloody stools. The differential diagnosis between sigmoiditis and angioneurotic edema of the intestines may be determined by the facts that in sigmoiditis there is a tendency to diarrhea, the bloody stools are more profuse and the duration of the disease is much longer. Where diarrhea is a marked symptom there is excessive thirst, diminution in the urinary output and marked exhaustion.

Cases are reported in which the colicky pains are of such severity as to simulate a surgical disease and lead to unnecessary laparotomy. The temperature is often normal but may be moderately elevated. In some cases high temperature is present for a few days. Where the gastrointestinal symptoms are preceded or accompanied by skin manifestations in the form of urticaria or angioneurotic edema, the diagnosis is simple. Cases, however, are encountered in which the gastro-intestinal symptoms set in a few days before the skin manifestations, or there are no skin manifestations at all, making the diagnosis very difficult or impossible.

The symptoms have a great tendency to recur. They usually affect several members of the same family but not necessarily during the same time. The *familial relationship* is as a rule characterized by the fact that not all the members get gastro-intestinal symptoms at the same time. One member may have only skin and another one only gastro-intestinal manifestations. One of our patients was a woman who suffered from time to time with angioneurotic edema. One attack was accompanied by edema of the glottis which cleared up very quickly after the injection of adrenalin. One of her children suffered from attacks of asthma and vasomotor rhinitis, and another child from gastro-intestinal symptoms.

**Pathogenesis**—The pathogenesis of the disease is not definitely established. The studies of Cook, Walker, Rolleston, Widal, Walzer,<sup>34</sup> Gray<sup>35</sup> and others, show that this affection is probably due to protein sensitization. The hypersensitiveness to the proteins is as a rule acquired during life. The hypersensitiveness which is at first latent becomes manifest by protein intoxication. Very often it is not due to a single but to a number of proteins. Numerous experiments have been performed to prove that protein sensitization is a great factor in this disease. Of the many experiments recorded the one of Phillips is the most striking. Phillips fed a five months' old bulldog for the first time the protein of pork and this was immediately followed by vomiting, bloody diarrhea and edema of the skin. The symptoms lasted forty-

have hyperparathyroidism. The nature of renal involvement or the duration of symptoms cannot provide a safe guide. Although a number of patients in our series had multiple or bilateral renal stones, and often had had renal colic for many years, one patient (case 34) who had severe hyperparathyroidism due to parathyroid adenoma had had

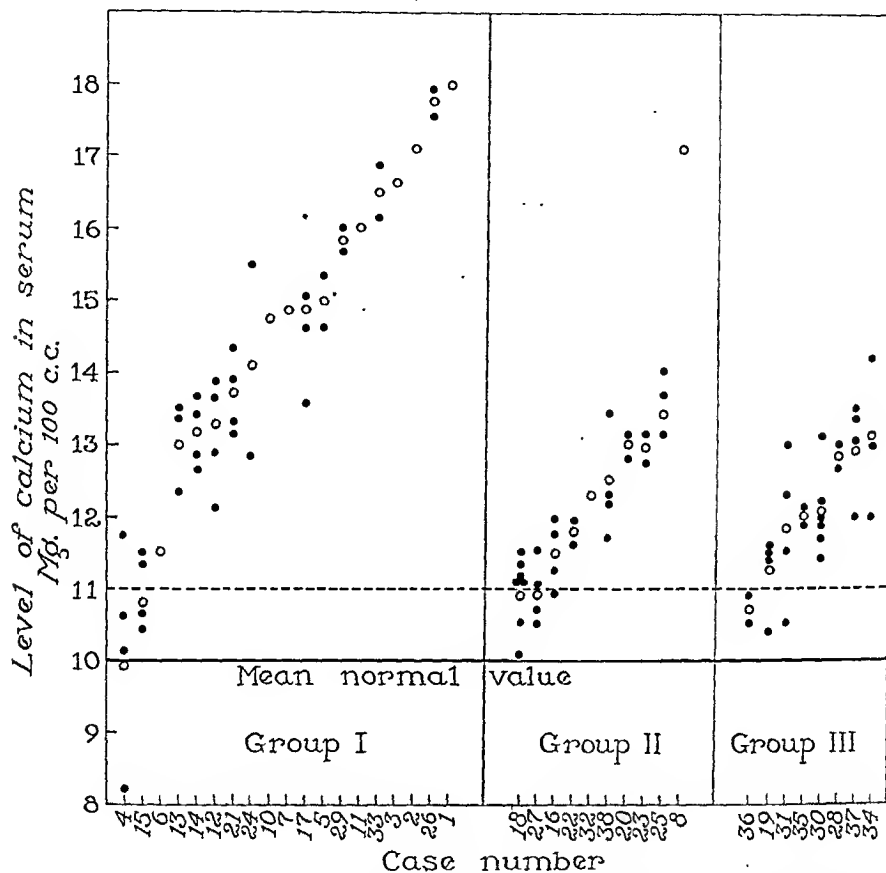


Fig. 154.—Range of values of serum calcium in thirty-seven cases of proved hyperparathyroidism. The cases are divided into three groups, as follows: Group 1, hyperparathyroidism with classic osteitis fibrosa cystica; group 2, hyperparathyroidism with demineralization or with minimal involvement of bone; group 3, hyperparathyroidism without disease of bone. Within each group the cases are arranged in order of average calcium values. Individual dots in each vertical line represent different determinations of serum calcium in a particular case; the white circles indicate the mean value of serum calcium in that case.

a single renal colic four months previously. In another case (case 22), the only symptom was a single attack of colic which had occurred twelve days previously.

The essential alterations common to all types of primary hyperparathyroidism are hypercalcemia, hypophosphatemia, hypercalcinuria and hyperphosphaturia.

dissecting aneurysm stage, the diagnosis does not suggest itself ante mortem. The most important symptoms are severe pain in the upper abdomen radiating to the lumbar dorsal vertebra. The pain is sometimes diffuse over the entire abdomen and may radiate to the left lower chest.

**CASE REPORTS**—In a case observed by us which we did not diagnose ante mortem, the patient, a nonluetic woman, about fifty-seven years old, had the following symptoms for several weeks: pain in the left hypochondrium radiating to the left side of the chest, moderate elevation of temperature and markedly diminished breathing over the base of the left lung and diminished respiratory mobility of the left side of the chest simulating pleural effusion or left subdiaphragmatic abscess. X-ray of the chest was negative. The persistent pain in the left lower chest and subdiaphragmatic region, the fluoroscopic finding of a high dome of the left diaphragm and the restricted mobility of the left dome of the diaphragm led us to insert a needle into the left subdiaphragmatic space because we suspected subdiaphragmatic abscess, but we did not obtain any fluid.

After several weeks, the patient suddenly went into shock, hemoglobin dropped to 40 per cent, and the blood pressure was so low as to be indeterminable. We therefore suspected that a rupture of a viscus, most likely of the stomach, with severe hemorrhage, had taken place. Blood transfusion and other restorative means failed, the patient died within a few hours. Postmortem examination showed a ruptured abdominal aorta with diffuse bleeding into the peritoneum. The pathologist, Dr. Plaut, likewise demonstrated that slowly dissecting aneurysm had preceded the rupture.

In another such case on our service a woman of sixty-two years gave a history of vague abdominal symptoms of six months' duration. About four weeks before rupture occurred she suffered severe intermittent abdominal pain requiring frequent administration of morphine. Attention was drawn to the possibility that symptoms were due to arteriosclerosis of the abdominal vessels by the fact that she frequently complained of coldness, numbness and pain of the lower extremities, the latter being more marked during the night. She also complained of severe pain in the back.

Anterior tibial and dorsalis pedis pulsation was diminished in both lower extremities, but more so in the left leg, though both feet were warm to touch. Pulsation of the femoral arteries of the left side was diminished. Oscillometric readings were not done. The pulsation in the perigastric region and to the left was extremely marked. Even without exerting any pressure with the stethoscope loudly diastolic and systolic murmurs were heard. Blood pressure was only moderately elevated and there was no vomiting. X-ray study of the gastro-intestinal aneurysm of the abdominal aorta which possibly was developing into the dissecting type.

The patient was on our service for about four weeks, when she suddenly went into shock with extreme abdominal distention, simulating peritonitis, and also marked anemia. She died within five or six hours. Our diagnosis of rupture of the abdominal aneurysm was confirmed at autopsy by Dr. Plaut, the pathologist.

total serum calcium is normal. Unfortunately, the values for the separate fractions of serum calcium cannot be determined directly but, if the values for the total serum calcium and the total serum protein are determined, the values for the separate fractions of serum calcium can be obtained by means of a nomogram devised by McLean and Hastings.<sup>34, 35</sup>

Determination of the concentration of the serum protein also is of value in distinguishing hyperparathyroidism from such diseases as multiple myeloma and Boeck's sarcoid, in which the concentration of serum calcium is increased owing to an increased concentration of serum protein.

*Hypophosphatemia.*—The accepted normal value for inorganic phosphorus in the serum is 3.5 mg. per 100 c.c., plus or minus 0.5 mg. The value for inorganic phosphorus is significantly lowered in cases of hyperparathyroidism and this change is more constantly present than is hypercalcemia.<sup>6</sup> Figure 155 shows the values for the inorganic phosphorus in the serum in the thirty-seven cases of parathyroid tumor. In three, or 8 per cent, of the cases, the average values were within the normal range. In eight, or 22 per cent, of the cases, the value was within the normal range on at least one occasion. In cases in which the diagnosis is questionable, the values for the calcium and inorganic phosphorus in the serum should be determined repeatedly in order to learn the significance of minimal changes which often are encountered.

*Hypercalcinuria.*—Sulkowitch has devised a test<sup>15</sup> which furnishes a rough estimate of the amount of calcium excreted in the urine. The test is performed in the following manner. Five cubic centimeters of an oxalate buffer mixture\* is added to an equal amount of urine that is acid to litmus paper. If the reaction is not acid, the urine should be acidified with a 50 per cent solution of acetic acid. The test tube is inverted and shaken, and the degree of turbidity produced by the precipitation of calcium oxalate is classified as grade 1 to 4. The urine of healthy persons who are receiving a diet that contains a normal amount of calcium will show a slight cloudiness (grade 1) whereas the urine of patients with hyperparathyroidism will show a greater degree of turbidity (grade 2 to 4). Unfortunately, if the urine of normal persons is concentrated or they have ingested excessive quantities of calcium (that is milk) it often will show a grade 2 or 3 response. It is important to eliminate dairy products and nuts from the diet for a day or two preceding the test.

Many patients with hyperparathyroidism have polyuria. Since the Sulkowitch test measures only the concentration of calcium, the large

\* The composition of the oxalate buffer mixture is as follows:

Oxalic acid .....	2.5 gm.
Ammonium oxalate .....	2.5 gm.
Glacial acetic acid .....	5 c.c.
Distilled water to make .....	150 c.c.



of place to state here that it would be a great humanitarian act and of considerable economic value if well equipped institutions for physical treatment were established in the larger cities where the poor could receive proper treatment for a small sum after working hours

If the symptoms indicate organic changes, such as erosion or ulcer of the stomach, appropriate treatment should be enforced. One should remember that in these individuals the organic symptoms are masked by the general nervous manifestations and we should not be misguided in treating these individuals as neuropaths which so often leads to disastrous results to the patient

**Dyspragia Intermittens Angiosclerotica Intestinalis**—The severe abdominal pains in dyspragia intestinalis are highly resistant to treatment. Morphine and atropine are indispensable in very severe attacks. For prolonged usage, a combination of papaverine 0.015 gm, aminophylline 0.15 gm and phenobarbital 0.03 gm, one capsule three times daily may be given, or one of the newer antispasmodics like syntropan, pava-trine or trasentin may be tried. When there is evidence of thrombosis of the lower extremities or thrombo-angitis obliterans the patient should be treated by one thoroughly equipped for the management of peripheral vascular disease. No experience has as yet been attained in the treatment of these cases by heparin intravenously, or by dicumarol, but they seem promising and might be attempted in these cases.

Meteorism is a very troublesome symptom. This should be treated by colonic irrigations and turpentine stupes. Pituirrin is not useful in these cases. Suppositories of codeine sulfate one half grain and luminal 2 grains, once or twice a day for a few days, will relieve pains. Vomiting is also a troublesome symptom and frequently gastric lavage must be resorted to, it is not contraindicated unless the blood pressure is very high. The diet should be restricted (strained barley soup, tea with milk, yolk of eggs, vichy). The symptoms very often disappear abruptly as in tabetic crises.

**Abdominal Angina**—The severe attacks of abdominal angina may be combated with nitroglycerin, by prolonged use of diuretin or other vasodilators (as aminophylline, phenobarbital, thesodate with phenobarbital), and physical and mental rest. Diet has very little influence but the patient should be cautioned to eat slowly and in small quantities and should be cautioned against foods that cause bloating, such as cabbage. Absolute inactivity should never be enforced except in advanced cases. Proteins should be restricted to 70 to 80 grams a day and a minimum of sodium chloride allowed. At times some anodynes, such as pantopon  $\frac{1}{3}$  grain, or papaverine  $\frac{1}{3}$  grain, must also be used for several weeks.

During the free interval, cases of abdominal angina are favorably influenced by carbon dioxide baths which are to be taken only under proper supervision. If the blood pressure is increased after these baths,

Aub.<sup>17</sup> The average excretion of calcium by most normal individuals who receive this diet is less than 100 mg. a day. An excretion of more than 150 mg. a day is considered highly suspicious by Albright, and values exceeding 200 mg. a day are regarded as definitely pathologic. Hypercalcinuria is not peculiar to hyperparathyroidism, however, as it may occur in other conditions associated with rapid demineralization of bone.

*Roentgenologic Appearance of Lesions of Bone.*—In cases in which the skeletal changes are minimal, the only abnormal roentgenologic finding is a mild diffuse miliary osteoporosis of the skull. In cases in

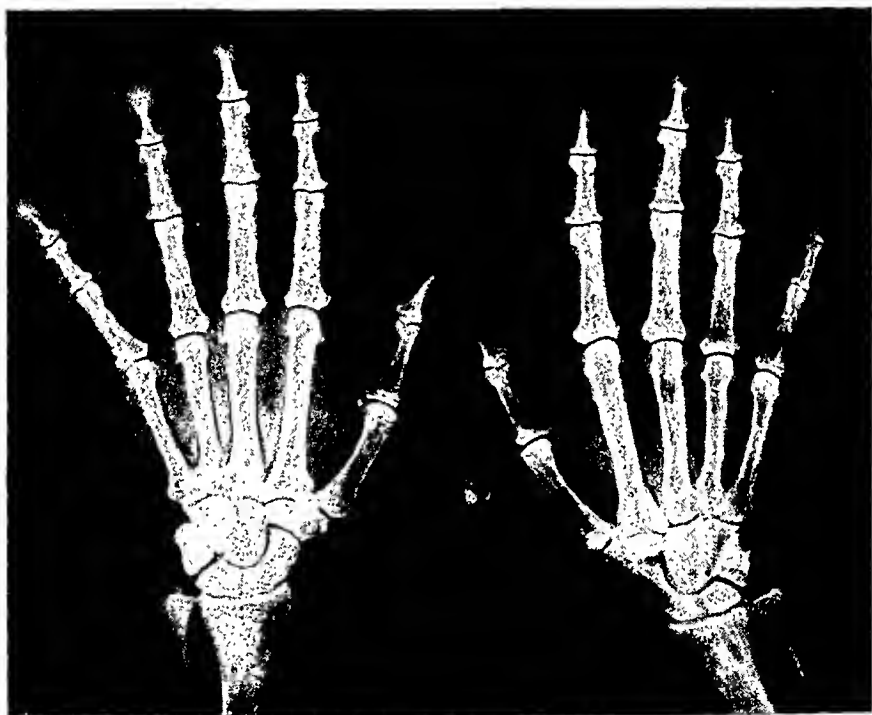


Fig. 157.—Roentgenologic appearance of the hand in case of hyperparathyroidism with classic bone disease. Generalized demineralization, coarsening of the trabeculae and subcortical absorption may be seen.

which the process is more advanced, there may be evidence of mild generalized demineralization, and subcortical resorption, most conspicuous in the extremities. More marked changes include fibrocystic disease, coarsening and widening of the trabeculae, thinning of cortical bone associated with generalized rarefaction of all bony structures, and the appearance of radiolucent areas in the shafts of long bones, the ribs and even the skull. The presence of large cysts and tumors may make the roentgenographic appearance of the skeleton most bizarre. The most important diagnostic criterion is that when pronounced changes are present in bone the entire skeleton is diffusely and visibly

ported by Litwins, Boyd and Greenwald as being valuable in the prolongation of coagulation

### CONCLUSION

In the angioneurotic or presclerotic state the psychosomatic symptoms are in the foreground, and it is important to remember that these are functional disturbances with a potential organic basis. The patients must be treated both as angioneurotics and as individuals requiring preventive measures. They are first of all subject to the development of peptic ulcer, which would call for a special preventative regimen.

It must not be forgotten that the symptoms due to sclerosis of the gastro-intestinal vessels or arteries may simulate even malignancy or they may simulate purely functional disorders and cause the patient to be regarded as a neurotic without any underlying organic disease. It is in precisely these cases that the psychosomatic approach is the correct one.

### SUMMARY AND CONCLUSIONS

1 A review of the symptomatology of the various conditions of the abdominal arterial system as well as some of the conditions that affect the veins is presented.

2 It is pointed out that many of these symptoms simulate diseases of the gastro-intestinal tract, the primary cause being confined to the blood vessels.

3 It is emphasized that arteriosclerotic changes in the abdominal aorta can be present simulating even carcinoma of the stomach.

4 Dissecting aneurysm and rupture of the abdominal aorta chiefly of an arteriosclerotic nature are not as frequently considered in the diagnosis as their incidence would warrant.

5 Periarteritis nodosa, with symptomatology confined to the abdominal viscera, is not unusual. Recognition of the condition when it affects a removable organ like the gallbladder or appendix is very important therapeutically.

6 As the degenerative changes in the blood vessels take place, there is first a period of angioneurosis, during which the symptoms are psychical in nature and reversible. In the period of transition, the symptoms become psychosomatic. Finally, the digestive organs are so deranged by the arteriosclerotic changes in the abdominal blood vessels that the symptoms are no longer amenable to treatment.

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also characteristic and may conceivably be evident as an earlier stage than similar changes elsewhere in the skeleton.

*Significance of Alkaline Serum Phosphatase.*—The determination of the concentration of alkaline phosphatase in the serum is of little value in the diagnosis of hyperparathyroidism. Alkaline serum phosphatase is apparently derived from osteoblastic tissue; in any event, an increase in alkaline phosphatase is nearly always indicative of accelerated osteoblastic activity. The concentration of alkaline serum phosphatase is a measure of disease of bone, not of parathyroid disease. In cases of osteitis fibrosa cystica, the value for the serum phosphatase usually is increased. In cases of hyperparathyroidism in which involvement of bone is minimal or absent, the value for the serum phosphatase is normal (2 to 4 Bodansky units).

*Diagnostic Criteria in Cases in Which Hyperparathyroidism Is Complicated by Renal Insufficiency.*—When renal insufficiency occurs as a consequence of primary hyperparathyroidism, it tends to obscure the characteristic chemical alterations of blood and urine. The concentration of inorganic phosphorus in the serum may be normal or increased and the degree of hypercalcemia tends to be less marked than it is in cases in which renal insufficiency is not present. Albright clearly demonstrated this in a case in which data were obtained before and after a serious degree of urinary insufficiency had developed.<sup>8</sup>

The excretion of calcium and phosphorus may likewise be reduced to normal proportions. This was illustrated in one case (case 15) in our series.

The patient was a woman, forty-five years of age, who had uncinat fits and very severe osteitis fibrosa cystica. As a result, innumerable pathologic fractures, many of them in bizarre sites, had occurred. Although symptoms of hyperparathyroidism had been present for only three years, she had a severe degree of renal insufficiency. The urea clearance was 12 c.c. per minute and the concentration of urea in the blood averaged 60 mg. per 100 c.c. Notwithstanding the extent of the involvement of bone, the average concentration of total calcium in serum was only 11.5 mg. per 100 c.c. and the average concentration of inorganic phosphorus was 3.0 mg. per 100 c.c. of serum. The excretion of calcium in the urine averaged 35 mg. per day. Excision of a parathyroid tumor effected a significant shift in the concentration of calcium and of phosphorus in the serum but apparently did not alter the renal disease.

The accurate diagnosis of mild hyperparathyroidism without disease of bone or with mild disease of bone remains exceedingly difficult. In considering the diagnosis in such instances, Albright stated, "If the serum calcium level itself is not sufficiently high to strongly suggest the disease, one can still be led to the right diagnosis if the serum phosphorus is persistently low, or if the calcium excretion is increased in the urine, or if the clinical picture fits the disease and no other disease. In this group, furthermore, it is important to do repeated determinations as the values fluctuate from the normal range into the definitely hyperparathyroid range."<sup>6</sup>

# MEDICAL OPHTHALMOLOGIC AIDS IN CIVILIAN AND MILITARY GENERAL PRACTICE

FERDINAND L P KOCH, M D \*

THE practitioner in general medicine and surgery whether civilian or military, because of wartime exigencies increasingly is encountering certain clinical problems other than those of traumatic origin. Such patients cannot always be referred to the special consultant because of the relative scarcity or inaccessibility of the latter. It is important, therefore, sociomedically as well as for the welfare of the individual patient, not only that deviations from the commonplace be recognized but that there also be familiarity with the diagnostic principles involved. This pertains to all specialty fields and is typically evident with regard to ocular manifestations of systemic diseases the examination, recognition and interpretation of which frequently are largely dependent on adequate ophthalmoscopy. Other clinical diagnostic procedures may be necessary and as careful a relevant history as possible is required for completeness. It is proposed to resurvey some of the old and new symptoms, signs and diagnostic procedures which may be applied from the standpoint of examination of the eyes.

## SYMPTOMS, SIGNS AND DIAGNOSTIC PROCEDURES

**Pain.**—Immediate attention usually will be sought for those dramatic medical ophthalmologic entities of rapid or sudden onset that are manifested subjectively by ocular or orbital pain or reduction in visual acuity or by both. Climactic episodes in chronic morbid processes will occur similarly, as will exacerbative incidents. Pain frequently is not precisely localizable or may be expressed only as discomfort.

**Central Vision.**—The level of visual acuity short of complete blindness always can be determined and, because of its potential medicolegal value, should be recorded in every instance of ocular complaint.

**Peripheral Fields.**—These should be examined and recorded wherever possible.

**External Examination.**—Presenting complaints may not be referable to the external structures but it is always advisable to examine the eyes and their adnexa from before backward to avoid overlooking local

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From the Department of Ophthalmology, College of Medicine, New York University and Bellevue Hospital

\* Assistant Clinical Professor of Ophthalmology, College of Medicine, New York University, Attending Ophthalmologist, Department of Ophthalmology, Third Surgical Division, Bellevue Hospital

centration of serum calcium may make the differential diagnosis simple in a given instance but one can imagine circumstances in which it might prove impossible to distinguish the two conditions. In adults, the roentgenologic appearance of the bones may be indistinguishable in the two conditions. In children, in addition to fibrocystic changes, there are broad irregular epiphyseal disks similar to those seen in true rickets.<sup>48</sup>

Some idea of the complicated relationships which may occur may be obtained from a most unusual case reported with postmortem findings by Downs and Scott.<sup>27</sup> The patient, who died of urinary insufficiency, was found to have a parathyroid adenoma, hyperplasia of all non-adenomatous parathyroid tissue, demineralization of the skeleton and nephrocalcinosis. The alterations in the chemistry of the blood were suggestive of secondary hyperparathyroidism. The authors made the reasonable suggestion that the patient initially had primary hyperparathyroidism resulting from the hyperfunctioning parathyroid adenoma. They assumed that this induced nephrocalcinosis, with subsequent renal failure which led to the development of secondary hyperplasia of the nonadenomatous parathyroid tissue and secondary hyperparathyroidism superimposed on the primary disease!

**Other Diseases of Bone.**—Serious diagnostic difficulty occasionally may be encountered in cases of multiple myeloma, Boeck's sarcoid and rarely in cases of metastatic carcinoma of bone. In these conditions, the concentration of calcium sometimes may be increased. The concentration of inorganic serum phosphorus in these conditions is generally normal or increased. In multiple myeloma and in Boeck's sarcoid, the hypercalcemia is often, but not always, accounted for by the degree of hyperproteinemia. Biopsy, aspiration of bone marrow and the demonstration of Bence-Jones protein in the urine are often of great assistance.

In generalized osteoporosis, or primary atrophy of bone, demineralization is apparently related to failure of osteoblastic activity rather than to increased absorption of bone. The roentgenoscopic appearance of the skeleton differs markedly from that in osteitis fibrosa cystica. The process is generally most marked in the spinal column and pelvis and less marked in the skull and extremities, the reverse of the distribution generally encountered in hyperparathyroidism. The concentrations of calcium, inorganic phosphorus and alkaline phosphatase in the serum are normal. Apparently similar osteoporosis occurs after the menopause, in association with exophthalmic goiter and with Cushing's syndrome.

Osteitis deformans (Paget's disease) and atypical forms of Albright's syndrome<sup>9, 30, 33</sup> are focal, not diffuse, diseases of bone. Careful scrutiny of the skeleton usually discloses some areas of normal bone; such a finding effectively rules out the presence of hyperparathyroidism. The concentration of alkaline phosphatase in the serum may be in-

frequently is confused with the tonic pupil of *Adie's syndrome*. This is a benign disorder, or symptom complex, with absent tendon reflexes and tonic pupils. The implications of an erroneous diagnosis of central nervous system syphilis are obvious. The newer science of pupillography is worthwhile.

**Tonometry and Ophthalmodynamometry**—Intra-ocular tension, *tenderness and abnormalities of contour or shape* of the eye and its adnexa are ascertainable from palpation which is done only with gentle firmness. Since only the relative hardness or softness of the eye can be determined by finger palpation through the eyelid, a tonometer should be used for accuracy. Uniformity is assured by employing only one of several models available. Tonometry is most useful in glaucoma but variations in intra-ocular tension recorded in millimeters of mercury should be determined in all instances of intra-ocular bleeding, suspected or proven retinal detachment and intra-ocular tumor and in the rarely encountered ophthalmomalacia. Ophthalmodynamometry, although much touted abroad, is of little clinical value in its present stage of development.

**The Use of Magnification in Examination**—A stereoscopic loupe of the Berger type, a corneal loupe or a standard biconvex hand lens is used in combination with direct or oblique illumination to furnish focal magnification. More minute observation with living ocular biomicroscopy is effected with the stationary slit lamp or with a hand model when the former is not available. Anterior abnormalities frequently will be demonstrable by transillumination through the eyelids.

**Photography**—Photography of the anterior ocular segment and of the eyeground is secondary to examination and can be done only with specialized technics and apparatus, however, it often is desirable to record clinical pictures for teaching, research and medicolegal purposes.

**The Use of the Ophthalmoscope**—An electric ophthalmoscope will furnish illuminated magnification for study of the anterior ocular segment when other, more efficient means are lacking. Index finger manipulation will bring into the examining aperture an appropriate convergent lens of  $+8$  to  $+15$  or  $+20$  diopters on the rotating Rekoss disk. The more anterior the structure or tissue the greater must be the power of the lens required for delineation. Defects of the cornea will appear gray or black against a diffuse reddish background if the crystalline lens of the eye is not grayish because of cataractous changes but, as lenses of progressively lesser power are rotated into the aperture, the retina gradually comes in focus.

#### TECHNIC OF OPHTHALMOSCOPY

The interior of the living eye is observable by the method of indirect ophthalmoscopy and even occasionally by retinoscopy, but its

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the head be grasped as if it were an elusive sphere Lids may be retracted by a movable bridge of fingers and should be released every few seconds for corneal wetting

**Mydriasis and Miosis**—Pupillary dilatation is necessary when fixation of gaze cannot be maintained or when pupils are 2 mm or less in diameter Ophthalmic paredrine hydrobromide solution (1 to 3 per cent) is very effective, rapid and does not require instillation of a counteracting miotic in most instances It is inadvisable to instill mydriatics with cycloplegic effects solely for ophthalmoscopic purposes when other equally adequate dilators are available It should be borne in mind, too, that in the event of any untoward circumstance such as the onset of acute glaucoma, the practitioner who neglects miosis following mydriasis is legally liable whether he is a civilian or in the military forces Efficacious miotics are solutions of pilocarpine hydrochloride (1 to 2 per cent) and eserine salicylate (0.25 to 0.5 per cent)

**Ophthalmoscopic Accessories**—A small *pinhole diaphragm* with an opening of approximately 1 mm when placed over the focusing condenser lens of the ophthalmoscope will appreciably reduce the annoying "corneal reflex" caused by reflection from the bright convex surface of the patient's cornea The resultant round field of illumination on the retina and choroid closely approximates the diameter of the average optic nervehead (which is about 1.5 mm in linear terms) and is a convenient unit of gross measurement for topographic location of items of interest A retinal *graticule* cross-hatched in squares of known values may be incorporated in the ophthalmoscope and projected in shadow onto the retina for measurement purposes, however, this is not recommended for routine clinical use

**Bulbs or color filters** that alter color value experience acquired daily since infancy will only necessitate the hasty acquisition of new color standards Conversion of the round light field to a *thin light slit* is offered in some ophthalmoscopes to aid in determining the presence and amount of elevation or depression of the area under examination, in which case the slit will seem to project, or bend, forward or backward, respectively Accommodative relaxation and careful focusing, however, even by those who have never known normal stereopsis, yields the desired information quite as readily without this alleged improvement which is justifiable only in the more complex instruments

**Binocular ophthalmoscopes**, whether portable or stationary, afford a spurious sense of depth of field and supposedly heightened contrast, but the uniocular models are more universally useful especially if the illumination system is maintained at its maximal efficiency Lenses should be kept clean, battery replacement should be frequent and bulbs should not be used after the glass has begun to gray

**Examination of the Fundus Oculi in Children**—Eyes of crying infants and children will be held ahead more fixedly than if crying is lack-

## PROTECTION IN ROENTGENOSCOPY

JOHN F. BACON AND EUGENE T. LEDDY

GENERALLY speaking, protection in roentgenoscopy concerns the prevention of injury of persons working with or near the radiations coming from the x-ray tube; it includes the use of any and all means by which the intensity of these radiations can be reduced to that of the "tolerance dose." By "tolerance dose" is meant that quantity of radiation which may be received by a person repeatedly or at intervals without bodily injury. Actually, the term "tolerance dose" is inaccurate and some other term such as "safe dose" should replace it. The rays against which the roentgenoscopist must protect himself come from both the primary beam of the x-ray and the secondary scattering from objects in the path of the primary beam.

The basic ideas of using distance and absorptive shielding for protection against roentgen rays were evolved about the same time that dangers of superficial injury through indiscriminate exposure to the rays became obvious. At first, the injuries were thought due to electric effects, ultraviolet rays, platinum particles from the x-ray tube and personal idiosyncrasy, and red silk and thin rubber sheets were suggested as protective measures. Roentgen himself probably escaped being hurt because he conducted most of his experiments, which were mainly photographic, with the x-ray tube inside a metal box.

In April, 1898, the Roentgen Society in England began to collect evidence on the harmful effects of the roentgen rays. Progress on absorptive shielding was, however, slow and confused for some time and, owing either to carelessness or ignorance, injuries and death continued to result. The situation was aggravated during the first World War when many diagnostic sets used by the British Army were relatively primitive and a number of prominent roentgenologists became casualties. After this, aroused public opinion started the movement toward the better conditions existing today.<sup>7</sup>

In the consideration of present-day protection the men who use roentgenologic equipment and need safeguards must be divided into two distinct groups: (1) the well-trained roentgenologist and (2) the relatively untrained general practitioners, surgeons and others who in the course of their practice "do a little x-ray work." Protection is a vastly different problem for each group. This was strongly emphasized by Hatchette, who pointed out the much greater risk to the untrained man during operation of roentgenologic apparatus. Unfortunately, most of the information, warnings and recommendations are placed before the skilled men—those who need it least—rather than before those most likely to be hurt.

The injuries which may occur as a result of roentgen rays may be

**HYPERTENSION**—There exist a multiplicity of syndromes of suspected or known etiology in which systemic arterial blood pressure is increased, but more than 90 per cent of hypertensive cases are classifiable as essential, or primary hypertension, of varying degree from minimal benign to malignant. The remainder are renal, cardiovascular, neurogenic and endocrinologic in origin. In the pathogenesis of hypertension the most important, ophthalmoscopically, of the five or more major etiologic factors is increased peripheral resistance, since arteriolar hypertonicity and its progressive consequences may be viewed directly in the eyegrounds. These changes, with environmental modifications, are counterparts of those occurring in vessels of similar order of size throughout the body.

*Classification of Hypertensive Diseases*—Ophthalmoscopically some terminology with which the observer is familiar must be employed. Numerous classifications have been offered among which are those of Gifford and Macpherson and of Clay and Baird, however, that of Wagener and Keith appears to be the most uniformly useful since, although some patients may have to be observed many months for accurate classification, it usually is not difficult to distinguish clinically between their four categorical groups.

The term, *diffuse arteriolar disease with hypertension*, was suggested by Wagener and Keith to supersede others since it implies dynamic changes in the arterioles. Thus, patients in Group 1 have only minimal or mild smooth attenuation (hypertonicity) or sclerosis of the retinal arterioles. They are placed in Group 2 if the retinal arterioles exhibit moderate to marked sclerosis whether or not narrowing is present, however, if sclerosis is of the chronic type, there is exaggerated arteriolar reflex striping and arteriolar-venous compression or, if sclerosis is postangiospastic, there is both generalized and localized irregular narrowing (beading) or attenuation of the arterioles. It is in this group that there will occur retinal venous thrombosis or retinitis, or both, of the arteriosclerotic type. Cottonwool exudates, edema of the retina and retinal hemorrhages all in combination with sclerotic and spastic arteriolar lesions characterize Group 3 patients, while those with a similar fundus picture but with superadded, measurable edematous elevation of the disks (malignant hypertension) are classifiable as Group 4. The prognosis for life expectancy becomes progressively serious from group to group. It is most grave in Group 4.

**RETINITIS**—Diffuse retinitis with edema of the disks and actively spastic arteriolar attenuation, all of acute or rapid onset, is an acute vasospastic disease and is familiar in the hypertensive toxemia of pregnancy, although it also occurs in men and nonpregnant women. Absorption of the retinitis may ensue, but if the vasospasticity as an expression of abnormal vascular physiology subsides before the onset of the initial retinitis, anatomic changes in the vessel walls usually will not

shielding and (3) operating procedures. Of these, the last is considered most significant.

In a study of 135 physicians who came to the Clinic between 1919 and 1935 for advice about or treatment of roentgen ray injury, Rigos and one of us. (E.T.L.)<sup>10</sup> found that ninety-one had contracted their injuries during reduction of fractures with the roentgenoscope. Of this number, seventy-eight admitted the use of no protection and eleven began to use lead rubber gloves only after injury had become apparent. Some of these men thought the dermatitis was of an allergic nature, perhaps caused by some soap or disinfecting solution in the operating room. In some instances, after receiving injuries to one hand from overexposure, these men used the other hand, again without protection, and suffered similar injury to it. Injury was recorded both from prolonged exposure at one examination and from cumulative effects of repeated unsafe doses. Of the 135, only eight had had any roentgenologic training, and all these eight had failed to follow the recommended measures of protection until they had been injured. The best protection untrained men can have during their work in reducing fractures under roentgenoscopic control is the presence of a roentgenologist to guide them. If this is not possible, observation of the following rather simple rules will cut the number of injuries markedly:<sup>9</sup>

1. Know the output of the machine and the time it takes the machine in operation to reach an output of roentgen rays which represent the limit of safety to the skin. Calibration of the tube in r per minute is essential.<sup>12</sup>

2. Use an aluminum filter at least 1 mm. thick.

3. Determine the lowest intensity of rays which allows satisfactory visualization. The technic may consist of factors such as 55 KV, 3 Ma, an aluminum filter 2 mm. thick, and a distance of 16 inches (40.6 cm.) between the tube and the top of the table in the reduction of average fractures of the extremities.<sup>13</sup>

4. Be certain of thorough "dark adaptation" of the eyes. This is a common source of failure on the part of men who "do a little x-ray." Not having become sufficiently or at all well adapted they need a considerably greater intensity of beam to see reasonably well. Patience is the secret of success here.

5. Wear lead rubber gloves and manipulate the fragments with the hands outside the beam as much as possible. This is most important. In spite of their clumsiness, bulkiness and general inconvenience, lead rubber gloves should be worn during all stages of roentgenoscopic reduction of fractures. It is obvious that the backs of the fingers and hands are most severely injured during such procedures. The thumbs are protected from the beam by the limb of the patient. This being the case, it is inevitable that at some time during the manipulation the backs of the hands come into the direct beam with little or no protection if gloves are not used.

considered indicative of diabetic nephritis but now is believed representative of intercapillary glomerulosclerosis

**Disorders of the Blood**—Blood dyscrasias do not manifest themselves diagnostically as typically as do the vascular diseases Pallor of the disk and choroid in anemia is diffuse as is that of arterioles and veins, however, there usually is a tendency toward approximation in color and lessening of contrast between the two types of vessels As hemoglobin values progressively decrease below about 70 per cent, pallor becomes more evident and retinitis may ensue This is characterized by thin, scattered, infrequent, superficial, cottonwool patches, slight diffuse retinal edema and pale, flame-shaped hemorrhages of varying size Hemorrhages are thick and "purpuric," however, and may be subhyaloid or preretinal when the platelet count is abnormally low as in aplastic anemia

White or grayish centers in hemorrhages, particularly in *leukemia*, are believed to be due to the relatively higher concentration of white cells compared to red cells in the blood *Chronic myelogenous leukemia* with high white counts gives rise to a fairly characteristic ophthalmoscopic picture in which there are leukocytic infiltrations in and about the vein walls especially in the retinal peripheries Marginal, flat, diffuse hemorrhages may be seen Veins are dilated and tortuous and present a dull anemic or peculiarly lipoid appearance which also is present to some extent in the arterioles This is in marked contrast to the cyanotic dilatation of the vasculature and cyanosis of the disk in *polycythemia vera* Extreme *vitamin deficiencies* from whatever cause frequently are accompanied by thin, sheet-like hemorrhages and there may be a low grade optic or retrobulbar neuritis

**Generalized Infections**—*Septic retinitis* arising from a systemic inflammatory disease seldom is diagnostic of its origin Cottonwool exudates or hemorrhagic areas, or both, may occur in diseases of known or unknown etiology with a septic type of fever Blood cultures may be negative or there may be only a transient bacteremia from time to time, rather than a septicemia In *subacute bacterial endocarditis* only hemorrhages, although of many varieties, may occur either singly or in groups or successively These petechiae may be accompanied in severer phases by edema of the disks, some cottonwool patches and hemorrhages with white centers Exudates, hemorrhages and edema may occur in *dermatomyositis*

*Acute, disseminated lupus erythematosus*, a disorder of metabolism of the collagenous tissue, results in the eyes in eventual primary optic atrophy on occasion because of progressive vascular closure proximalward from the less vascular retinal peripheries Phlebitis and arteri-olitis together with fine, superficial hemorrhages in the immediately focal choroidal exudates *Virus infections*, if severe, and *acute parasitic*

part for the false sense of security possessed by many "men who do a little x-ray work." Much information is spread concerning the shock-proof nature of the machine, its ease of operation and excellence of performance, but never—or at least seldom—in this advertising can one find warnings about the risks that the physician takes in operating the machine. One cannot condemn the manufacturers of the apparatus, however, since they are no more bound to teach physicians how to operate the machines than are automobile manufacturers expected to teach purchasers how to drive.

It has been proved beyond question that the risks of injury sustained by the roentgenologic specialist are negligible in contrast to the high risk run by the casual user of roentgenologic equipment. The faults in technic by which an inexperienced or careless operator may exceed the limits of safety to himself may be summarized as follows:<sup>8</sup> (1) lack of technic of examination; (2) excessive "puttering around"; (3) incomplete adaptation of the eyes to darkness; (4) too much current and voltage; (5) insufficient filtration in the roentgenologic apparatus; (6) use of too large fields; (7) placing the bare hand in the field; (8) lack of lead rubber protecting gloves; (9) inattention to the time that the roentgen tube has been in operation and (10) ignorance of the protecting devices advocated by the Safety Committee.

Looking at the subject of protection from the point of view of the physician who uses roentgenologic apparatus, two general statements stand out. Training, common sense and experience are probably the three most important protective devices with which the operator can fortify himself. Carelessness and ignorance are the commonest causes of injury from irradiation. Ignorance is inexcusable because the recommendations of the safety committees are so clear and concise that all confusion concerning protection is out of the question. Carelessness, however, is a common human fault, but if one keeps in mind the potential danger to himself, to the patient and to the associated personnel, carelessness in protection will cease to be a cause of injury. The recommendations of the safety committees should be known by everyone and, being known, should be meticulously observed.

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## ROCKY MOUNTAIN SPOTTED FEVER

GEORGE E BAKER, MD, FACP\*

SHORTLY more than a decade ago the belief was general that Rocky Mountain spotted fever was limited in distribution to the Rocky Mountain states and portions of adjacent areas. When as a medical student I attended a midwestern university, the disease there was given but cursory attention, scant heed being paid to it in the teaching curriculum. For some reason discussion of Rocky Mountain spotted fever was included with that of tropical diseases. An instructor familiar with those entities, but who I am sure had never attended a case of Rocky Mountain spotted fever, lectured briefly on the supposed bizarre disease entity.

Having resided in Wyoming nearly all my life, I had frequently observed an illness which afflicted rural residents, chiefly ranchers and stockmen, during the spring and early summer months. The infection was commonly called "tick fever." It was apparently one of the gravest significance, inasmuch as deaths resulting from it were frequent. During my medical school days it often occurred to me that Rocky Mountain spotted fever and "tick fever" might be the same disease. Unfortunately there was but little factual information in standard medical textbooks. Some of them, it is true, in brief pages devoted to Rocky Mountain spotted fever seemed to lend the impression that there was marked similarity between the two infections, or that they were the same disease.

Upon my return to Wyoming to practice, it was my good fortune to be associated with an older physician, who as a result of many years of practice in the state had thoroughly familiarized himself with Rocky Mountain spotted fever. It was not long before I realized that the terms referred to the same entity, the name "tick fever" being applied to it by western residents for the sake of brevity. As a matter of necessity, I soon learned much of various phases of the disease. I found that many western physicians were well versed on Rocky Mountain spotted fever, but that only a few of them had taken advantage of an opportunity to describe the illness. Clinical observations were often confusing and contradictory.

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\* Chief of Staff and Chief of Medicine, Memorial Hospital of Natrona County, Casper, Wyoming

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## THE IMPORTANCE OF DIAGNOSING CHRONIC SUBDURAL HEMATOMA

PHILIP H. HEERSEMA AND JOHN G. FREEMAN

SUBDURAL hematoma has long been recognized as a concomitant or sequel of injury of the head. Because the treatment of this condition has resulted in complete recovery in a high percentage of cases, the condition automatically has been allocated too readily to the sphere of the surgeon, and even more specifically to the neurosurgeon, whereas in confusing cases in which there is no history of trauma the condition may not even receive surgical attention unless the internist is particularly alert. Contributions to this subject within the past twenty years have been preponderantly those of surgeons, which tends to create the impression that the diagnosis of subdural hematoma is primarily a surgical one. Actually, in very many cases of subdural hematoma the disease may be sufficiently confused with nonsurgical inflammatory and cerebrovascular syndromes to make surgical consultation seem superfluous. Therefore, it seems that it is fitting that more emphasis be placed on making the diagnostician, that is, the internist and the clinical neurologist, more aware of the importance of consideration of this condition in cases in which there is evidence of progressive neurologic or mental defects without a definite history of trauma. Although a history of trauma may be elicited retrospectively or at least suspected, it becomes particularly important to proceed on the strength of certain signs and symptoms without an enlightening history if one is to obtain best results from treatment, for treatment is relatively simple once the diagnosis is considered and made.

There are various classifications of subdural hematoma. A simple classification includes three main groups; namely, acute subdural hemorrhage (rather than hematoma), subacute subdural hematoma and chronic subdural hematoma. In this classification, subdural hygroma, which is a posttraumatic collection of fluid resulting from a rent in the arachnoid, is listed as a subdivision of chronic subdural hematoma. This paper deals chiefly with chronic subdural hematoma because the diagnosis of this condition is very difficult and of course is the primary factor in management.

Munro reported 310 cases of subdural hematoma and classified the respective lesions in two main groups: (1) acute mixed subdural hematomas and (2) chronic subdural hematomas. The second group was divided into two subgroups; namely, fluid hematomas and solid hematomas. Under the heading of fluid hematomas, the author included the lesions which many authors have designated as hygromas. A mixed subdural hematoma contains both blood and cerebro-



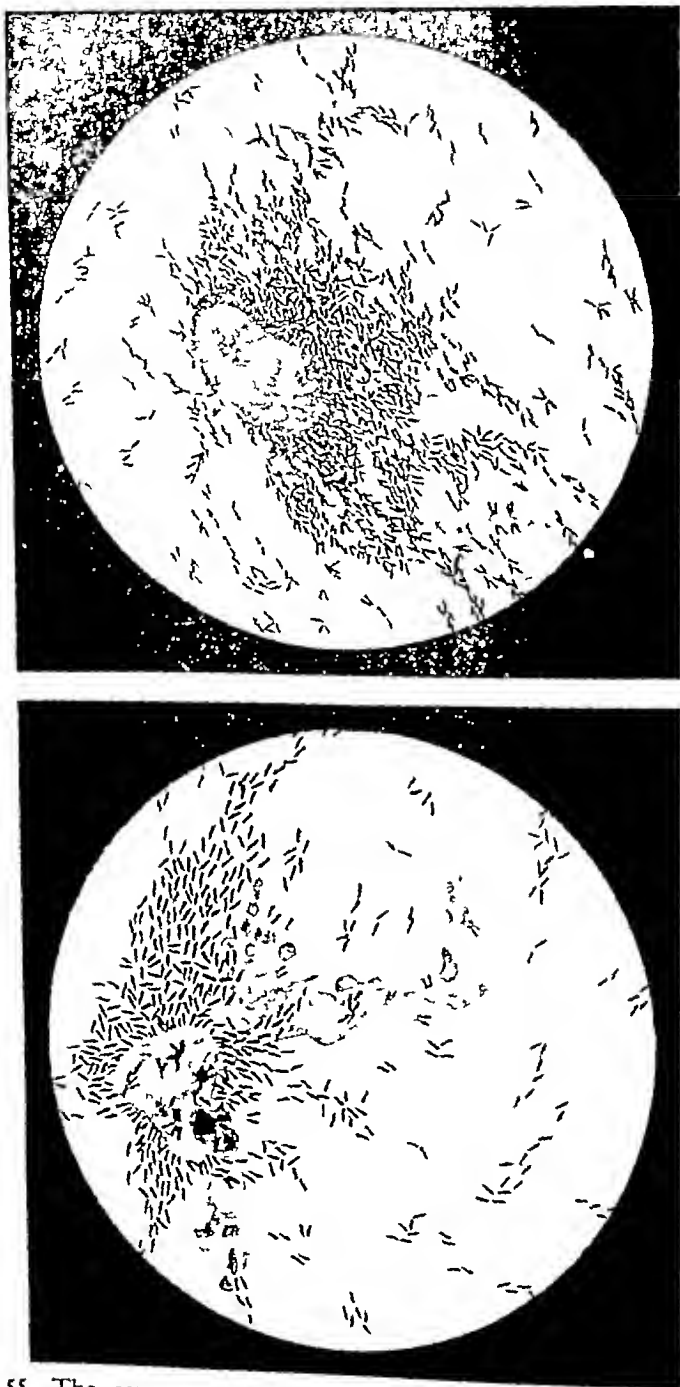


Fig 55—The causative micro-organisms of typhus fever (upper) and of Rocky Mountain spotted fever (lower) *Rickettsia prowazekii* of typhus fever is found chiefly in the cytoplasm of cells, while *Dermacentor venustus rickettsii* of Rocky Mountain spotted fever invades the nuclei also (Sharp & Dohme, Seminar, Vol 4, No 2)

It is encouraging to note the number of articles on subdural hematoma that have been published within the past twenty years. The literature on this subject is by no means voluminous nor is much to be gained by padding it in the future with reports of large series of cases except to impress physicians with the relatively frequent incidence of this disease and its importance as a clinical entity. However, reports of unusual cases, which enhance one's diagnostic acumen, are obviously valuable. This is exemplified by the two cases reported by McCall and Love. In one of these cases, the history, symptoms and clinical findings were typical. In the other case, however, there was a high degree of choked disk and the only history of trauma was that the patient had received a "ducking" while he had been swimming.

Although there were earlier reports regarding the relationship of the meninges to hemorrhage, it was Virchow in 1857 who first gave a clear histologic description of the reaction of the dura to hemorrhage and it was he who coined the term "pachymeningitis interna hemorrhagica." He entertained the idea that in certain cases the dura became chronically inflamed. He termed this inflammation "pachymeningitis interna chronica." He mentioned that it occurred among insane patients, but he failed to recognize that insane patients were particularly liable to injury. It was his opinion that an inflammatory process was responsible for the primary formation of a membrane which laid the foundation for oozing hemorrhage by reason of capillary growth into the membrane and a susceptibility of the capillaries to rupture. His opinion prevailed for many years and it was not until 1914 that Trotter advanced the idea that trauma easily could cause a rupture of the veins which bridged the space between the pia mater and the cerebral sinuses since these veins were relatively susceptible to rupture by reason of their sharp angulation and rigid fixation in relation to the longitudinal sinus. It was his opinion that even minor traumatic forces exerted in the proper direction could cause a hemorrhage and that the enclosing membrane subsequently would be derived from the organization of the outer layer of the clot. He was the first to emphasize the increased frequency of trauma among alcoholic and insane patients, in whom it was recognized that there was a higher incidence of subdural hematoma than in the average population. From the diagnostic standpoint, one of the most important contributions made by Trotter was his emphasis of the variation of the state of consciousness, which is of value in distinguishing subdural hematoma from tumor of the brain.

It might be said that the diagnosis of subdural hematoma reached its maturity in America with Putnam and Cushing's classic article which appeared in 1925. In this article, the etiologic importance of trauma was stressed, the pathologic and clinical aspects were considered and the operative treatment was reviewed. In 1932, Gardner advanced a plausible explanation of the latent interval in cases of chronic

ever the disease has appeared, native species have been isolated and their capabilities partially identified

The percentage of ticks that carry infectious virus has been studied mainly in the wood tick. It is different in different localities and from year to year in the same locality. However, even in areas known to be heavily infected the ratio of infected to noninfected ticks is very low. It has been estimated that this ratio, in heavily infected areas, is not more than 1/300. Were this not the case, the number of human beings stricken with tick fever each year would undoubtedly be much greater than it is.

When ticks emerge in the spring from hibernation their virus virulence is low, consequently few cases of Rocky Mountain spotted fever are seen for a few weeks or even a month thereafter. When subjected to incubation or allowed to ingest blood, the ticks gain the ability to bring about frank infections, due to an increase of virus virulence. The phenomenon is known as "reactivation." In nature, with the advent of warm weather, the ticks become quickly activated and more readily infectious. Reactivation can occur in the colder months of the year, granted that there is an abundance of warmth from rays of the sun or adequate conditions of artificial heat, which release ticks from their dormant state. They move about in search of hosts. Within a short while their virulence is increased and infection of human beings can result.

Rocky Mountain spotted fever appears to have a cyclic tendency, more cases appearing during some years than others. The reason for the trend is unknown, but it is believed to depend on local and regional conditions. The number of individuals exposed, the abundance of ticks, the percentage of ticks carrying infection, the capability of virus to produce frank infections and the possible relationship between the prevalence of ticks and animal hosts seem to play a part.

Rocky Mountain spotted fever is not primarily a disease of human beings, but is one of animals and would exist if the former were eliminated from the picture. Ticks are not parasites of the human race. When individuals are bitten, the occurrence is purely an accident. The animals which contribute to perpetuation of Rocky Mountain spotted fever virus in nature by serving as tick hosts are not the same in every locality. It seems possible that those most commonly concerned in transmitting the infection from tick to tick are several species of small wild rodents. Those which serve as hosts for larvae and nymphs of wood ticks are also susceptible to infection. Their dual function is largely responsible for perpetuation of tick fever in the Rocky Mountain region. Apparently they are capable of playing a similar role wherever they are found. The larger wild or domestic animals are not susceptible to frank infections.

It is believed that the virus may be transmitted from one tick to

exposure, and the angle of their attachment to the sinus, they are more susceptible to trauma than other vessels of the brain or meninges. Likewise, this may be a reason why so-called spontaneous subdural hematoma also occurs in these sites since these veins are subjected to some type of blood dyscrasia or surrounding inflammatory reaction as a part of general vascular affection and may be rendered so susceptible that activity considered to be entirely normal might be sufficient to result in spontaneous hemorrhage.

The limiting membrane of a subdural hematoma still is a controversial subject. Certain neurosurgeons have cast doubt on existence of an intradural hematoma by stating that they never have seen one. This presupposes that the limiting membrane is the product of the clot and that fibroblasts grow out from the leukocytes or from the neighboring meninges and produce the limiting membrane. This fits in much more closely with the theory that trauma always is an etiologic factor. The adherents of the theory that the limiting membrane of the clot is actually a part of the dura which is split off and that the hematoma is actually intradural also offer some very sound arguments. Baker, for instance, in adhering to this intradural theory, raised the following question: If the clot is subdural and the membrane is formed from the dura (that is, after the clot has occurred on the dura), why would the various cells go all the way to the inner or arachnoid surface of the clot and form a membrane rather than produce a gradual progressive organization of the entire clot? Yet, aside from the encapsulating membrane, the dura may be perfectly normal and remain so after evacuation of the clot. In our opinion, the incidence of both traumatic and spontaneous hemorrhage can be more satisfactorily explained on an intradural rather than a subdural basis. However, it is not the purpose of this paper to deal with the academic aspects but rather to emphasize the practical clinical features of this interesting clinical entity.

#### MATERIAL

This paper is based primarily on twenty-five consecutive cases of chronic subdural hematoma that were observed at the Clinic in a period of thirty-five months, that is, between January 1, 1941 and November 30, 1943, inclusive. In all of these cases, the diagnosis was proved by operation or necropsy at the Clinic. In general, this series of cases furnishes a concise picture of our experience with chronic subdural hematoma. This series does not include any case in which the patient was an infant. Subdural hematomas of infants comprise a special field. Their diagnosis and treatment have been summarized very well by Ingraham and Matson. The differential diagnosis of chronic subdural hematoma is the problem of the internist. On the other hand, in cases of acute subdural hematoma (hemorrhage), the surgeon should decide when trephination alone or in combination with ventriculography or encephalography should be performed.

blood vessels of the skin, is responsible for the cutaneous and subcutaneous hemorrhages. Other features of the eruption are explained by the occurrence of occluding thrombi in the small arteries and veins.

The changes brought about by the disease are so typical that spotted fever, from a pathological standpoint, may well be called a condition of the peripheral blood vessels, or an acute specific endangitis. The minute causative micro-organism may be demonstrated with considerable difficulty in the blood vessel walls in the endothelium and smooth muscle fibers of the media in relationship to thrombi.

#### INCIDENCE

**Geographical**—The average number of cases of Rocky Mountain spotted fever reported each year in the United States is 450 to 600. The disease has been detected in forty-two states, the exceptions being Connecticut, Maine, Michigan, New Hampshire, Rhode Island and Vermont. Western states show the highest incidence, of these the Rocky Mountain states claim the highest number. In the eastern states the disease is found with the greatest frequency in the states of Maryland, North Carolina and Virginia.

It is not known whether Rocky Mountain spotted fever was originally a disease of the eastern and southeastern sections of the country, carried from there westward by tides of emigration, or one of the West, brought eastward by more rapid means of communication at the turn of the present century. It is believed by most authorities that the disease was never absent from the western states. Accidental transfer of wood ticks to the eastern and central states by means of livestock or other animals shipped from the Rocky Mountain region has not resulted in establishment of the tick or virus in nature in those localities. If the virus of the disease as encountered in dog ticks had been derived from ticks of the Rocky Mountain states, a clearly defined trail along lines of transportation should be found. Investigations have failed to reveal that such routes of dissemination exist, although stock has been shipped eastward over railroads and highways for a period of many years. Because there is no proof to the contrary, it must be assumed that Rocky Mountain spotted fever is indigenous to the locality where it is found.

**Season**—The yearly peak of incidence of Rocky Mountain spotted fever coincides with the tick season in the locality concerned. In the western endemic regions, the wood tick appears in February. It can be found in small numbers as late as August and September, but it is most prevalent from the middle of March to the middle of June. The disease occurs with the greatest frequency from March to July, with occasional cases up to October. The dog tick in the East appears in March. It is most abundant from May to July, but has been found as late as November and December. The disease in the East is reported

vary from a lapse of memory to aberrations of behavior or frank coma. This change is of great importance in making a diagnosis of chronic subdural hematoma. It is not unusual for a semicomatose state or mental stupor to develop in a few days or even within a few hours. For a number of days preceding this change in the state of consciousness there will be a defect in memory or orientation. The change also may be preceded by headache, drowsiness, vertigo, nausea and vomiting.

TABLE 2.—PRINCIPAL PHYSICAL SIGNS AT TIME OF INITIAL EXAMINATION AT THE CLINIC

Physical Signs	Cases	
	Number	Per cent
Slow pulse rate (below 70).....	14	56
Choked disk (less than 2 diopters).....	9	36
Hyperreflexia, bilateral.....	8	32
Hyperreflexia, unilateral.....	1	4
Hemiparesis and spasticity, bilateral.....	6	24
Hemiparesis and spasticity, unilateral.....	3	12
Babinski's reflex, bilateral.....	6	24
Babinski's reflex, unilateral.....	3	12
Paresis of oculomotor nerve (ptosis of upper eyelid)	5	20
Paresis of oculomotor nerve (limitation of movement of eyeball).....	2	8
Paresis of facial nerve.....	5	20
Unilateral enlargement of pupil (both pupils were homolateral).....	2	8
Stiffness of neck.....	1	4

Symptoms that are due to the pressure of the hematoma on adjacent structures do not occur consistently. Diplopia, ocular palsy, hemiparesis and jacksonian epilepsy usually do not occur until the condition of the patient becomes critical.

In the majority of the cases in which the patients were conscious when they came to the Clinic, the symptoms and signs were of a mild character. If only a cursory examination had been performed, it is entirely possible that, in some cases, treatment might have been di-

ache, anorexia and chilling sensations. These vary in degree, lasting two or three days and resemble in many respects the invasion of any febrile illness.

**Onset**—Onset of the disease is usually abrupt, coming as a rule in the late afternoon or early evening. It is manifested by the occurrence of a definite chill, pronounced frontal or occipital headache and severe aches and pains in the muscles, bones and joints. Aches and pains are more pronounced in the back and lower extremities. Movement of the calf muscles or firm pressure over them often elicits pain. Inspection may reveal the presence of crawling or attached ticks. Usually, however, none is found, since it is customary for the patient to remove them before reporting for care. Indurated sites of former attach-

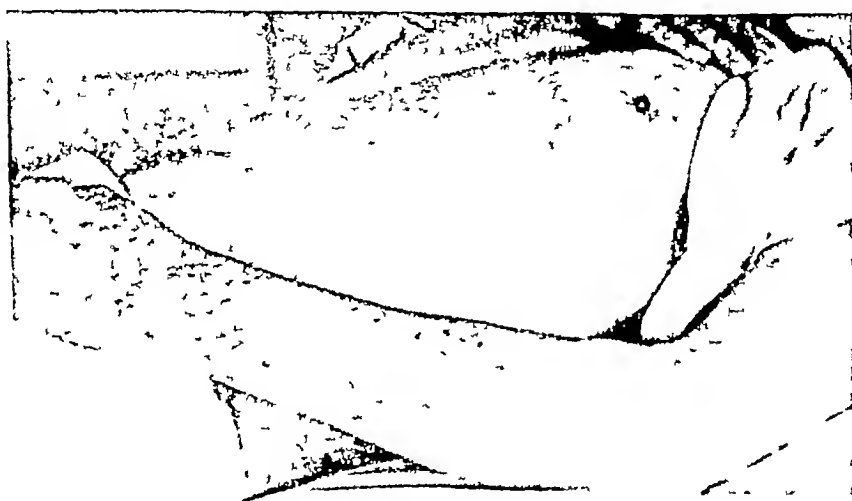


Fig 57—Eruption of the left lateral chest and left arm in a moderately severe recovered case of Rocky Mountain spotted fever. The lesions are discrete and most marked on the hand and wrist.

ment may be detected. The bite areas show no peculiarities, although in some instances they may appear discolored from subcutaneous blood extravasation. The regional lymph nodes are at times palpable and tender.

**The Rash**—Sometimes there is an initial mottled appearance of the skin of the face, neck and upper chest. It is by no means constant in character, but may simulate the onset of measles, particularly in fair-skinned individuals. The characteristic eruption, typical of Rocky Mountain spotted fever, is seen on the second to fourth day of the disease. Its appearance may be delayed until the fifth or sixth day. It is first detected on the flexor surfaces of the wrists and ankles. The rash is macular to begin with but later it becomes maculopapular. Definite petechiae may be formed.

between the trauma and the appearance of symptoms, the etiologic role of the trauma should be seriously discounted.

There is little relation between the degree of the trauma and the development of a subdural hematoma. In our experience, it seems that a subdural hematoma is more likely to follow a slight injury of the head than it is to follow a serious injury. In this connection, we might add that we wish chiefly to emphasize the diagnosis of chronic subdural hematoma in cases in which there is no history of trauma.

The chief value of examination of the cerebrospinal fluid in cases of chronic subdural hematoma is to rule out the presence of an inflammatory disease. In one case in this series, repeated cytologic and chemical examination of the cerebrospinal fluid disclosed changes that were suggestive of a chronic inflammatory disease but the pressure of the fluid was higher than it is in chronic inflammatory disease and indicated the need for surgical intervention.

In five (20 per cent) of the cases in this series, roentgenographic examination of the skull disclosed that the pineal gland had been displaced to one side. In four of these five cases, this finding was confirmed at operation. The diagnosis may be confirmed by encephalography or ventriculography but neurosurgeons generally are critical of these procedures. Bucy actually suspected that pneumo-encephalography was instrumental in causing a subdural hematoma in one case. Some authors believe that the removal of some cerebrospinal fluid and its replacement with air may interfere with the dynamics of the cerebrospinal fluid sufficient to add to the gravity of the situation in the case of a spatial lesion of the brain.

In half of the cases in this series, electro-encephalography disclosed unilateral delta waves, which aided in localizing the lesion. Rogers said that in his cases of chronic subdural hematoma the electro-encephalogram tended to be of the low potential type but this has not been our experience. In our series of cases, electro-encephalography disclosed generalized delta waves in the affected region but in some cases this finding was too extensive to be of any localizing value. In 38 per cent of our cases, electro-encephalography disclosed generalized delta waves or bilateral delta waves. The extent of the abnormal graph was not unexpected as a hematoma frequently involves an entire hemisphere of the brain. In the remaining 12 per cent of the cases, the electro-encephalograms were normal, which finding must be considered erroneous.

**Differential Diagnosis.**—*Tumor of the Brain.*—In cases of tumor of the frontal lobe, there may be a definite change in personality but this develops gradually and insidiously. In cases of chronic subdural hematoma, irritability, mental confusion and disturbances of the sensorium usually develop abruptly.

In cases of subdural hematoma, the symptoms vary; in cases of tumor of the brain, the severity of the symptoms increases progres-



of the hands, soles of the feet and scalp. The mucosa of the inner cheeks, palate, fauces and pharynx may not escape. The eyelids can be involved. The rash is always more pronounced on the extremities than elsewhere on the body. The lesions on the face and abdomen are usually not abundant. Extension is complete in two or three days. The associated generalized aches are relieved to a degree but temperature remains high.

The maculopapular eruption is thought to be the most characteristic finding in tick fever, but diagnosis of the disease must not be made on its presence. Some patients, particularly those only mildly affected or those previously vaccinated, never show a rash or show an insignificant one, others die from toxemia before its appearance, and yet others demonstrate atypical or bizarre eruptions. The lesions do not disappear on pressure except during the initial stages. They are accentuated by tourniquet application. The completely erupted patient is truly speckled or spotted, having a rash that covers the entire body. Lesions may appear in successive crops, each of which has an average life cycle of two weeks.

The eruption tends to remain discrete in milder cases of tick fever. It is first rose red and later bluish red, circumscribed and sharply demarcated, with intervening clear areas of skin. Discreteness does not persist in more severe cases. The lesions increase in size and become confluent, finally coalescing and then becoming purpuric (Figs 60, 61). A mass of such areas may involve the entire body. If terminal gangrene ensues, with sloughing of the mucous membranes of the soft palate, skin of the ear lobes, vulva, toes, fingers, prepuce, buttocks or other dependent body parts, the afflicted individual presents a pathetic appearance.

The eruption gradually fades as patients recover. Fading takes much longer in severe cases than in mild ones. It occurs with the fall in temperature. There may be desquamation, either branlike in character or so complete that casts of body parts are exfoliated. Pigmentation remains at former eruption sites. It may be followed by the formation of minute cicatrices. For several months following recovery from Rocky Mountain spotted fever, overexposure to heat or cold often brings out temporary manifestations of the lesions. They last only a short while and clear when skin temperatures again return to normal.

**The Fever**—Temperature rises abruptly within the first twenty-four hours of the onset of the disease. There are but one or two slight remissions, a fastigium of  $103^{\circ}$  to  $105^{\circ}$  F being reached by the beginning of the second week in mild cases, by the second or third day in more severe ones. With recovery from acute manifestations of the illness, it falls either by rapid or slow lysis, rarely by crisis unless the case is an abortive one. There may be slight temperature remissions in mild cases, but it is constant to slightly rising in more severe ones. It

cerebrospinal fluid is otherwise essentially normal, a subdural lesion probably is present.

*Syphilis of the Central Nervous System.*—In cases of syphilis of the central nervous system, the diagnosis usually can be made by means of serologic tests.

*Other Lesions of the Brain.*—In cases of meningitis and abscess of the brain, there is a febrile reaction and the diagnosis usually is aided by examining the blood and cerebrospinal fluid, in addition to the infectious features of the history.

#### COMMENT

Death occurred in three of the cases in our series but none of the deaths could be attributed to operation. In two of the three cases, the patients were not referred to a surgeon. In these three cases, the patients were more than sixty years of age, that is, at the age at which confusing vascular syndromes are likely to occur. In sixteen of the twenty-two cases in which the patients survived, the results were very good. In at least a third of these cases, the physical condition of the patient returned to normal within a month. In three cases, the patients were having occasional attacks of convulsions when the last follow-up data were obtained. One patient had mild hemiparesis and spasticity. Another patient had periods of aphasia but his condition subsequently improved. In one case, a severe anxiety state occurred after operation.

Bilateral hematomas were found in three (12 per cent) of the cases. This incidence of bilateral hematomas is slightly lower than that reported by some authors but it is high enough to warrant consideration in every case of suspected subdural hematoma.

In most cases of chronic subdural hematoma, the patients withstand trephination better than they do encephalography. In cases in which the presence of a subdural hematoma is suspected, trephination, followed by ventriculography if necessary, is superior to the preliminary introduction of air in making a diagnosis.

Special consideration of the diagnosis of chronic subdural hematoma should always be given, especially if the patient is aged, in the suspected case of intracranial lesion in which variations of mental alertness are noted, the neurologic signs are likewise variable, the headache is persistent and the entire course is relatively brief. This also holds true in those cases in which a history of trauma has not been elicited.

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twenty-four hours preceding death, or it may be high from the first, then drop to normal and rise again before death occurs. If the temperature drops uneventfully to normal and later shows a secondary rise without apparent justification, complications must be sought for.

**Pulse and Respiration**—Early in the disease the pulse is of good volume. It is slow, averaging 90 beats a minute. Early disproportion of pulse and temperature ratios is one of the characteristics of Rocky Mountain spotted fever at its onset. When myocardial weakening ensues in severe cases as a result of toxemia, loss of strength and volume of the pulse occurs. It rises out of proportion to the temperature. As a result of cardiac involvement, the blood pressure falls and the first heart sound becomes muffled and indistinct. The occurrence of pulmonary edema often portends a fatal termination within a matter of hours.

The respirations are at first normal or but slightly increased. They accelerate in severe cases, with alterations of the pulse and temperature ratio. Increase in rates often signify the development of pneumonia. Terminal temperatures of  $106^{\circ}$  to  $108^{\circ}$  F, pulses of 140 to 160 and respiration rates of 40 to 60 are not unusual.

**Miscellaneous Findings**—The foregoing manifestations are considered to be the most typical ones in tick fever. There are other findings. They exist in various combinations, their intensity often depending on the severity of the existent disease process.

Patients moderately or severely ill with tick fever are severely *prostrated*. The senses are dulled. Although afflicted individuals appear rational to superficial examination, close inspection reveals that they are *mentally confused*. There is *amnesia*. It may persist until the eruption is complete or for some time afterward. Patients appear *anxious and concerned* over their illnesses. The eyes are reddened and lack their normal luster. The cheeks are flushed. There may be *photophobia* or sensitivity of the eyes to pressure.

*Nervous disturbances* such as lethargy, restlessness or nervous irritability are frequent. Children are prone to convulsions and may die during them. Insomnia is at times troublesome. There can be active delirium, particularly in severe cases during the terminal stages of the illness. *Muscular twitchings* and fibrillatory tremors are common. *Muscle tonus* is definitely increased throughout the body. *Aches and pains in the muscles* persist throughout the disease. At times the distress from them is agonizing. When located in the muscles of the abdomen an acute surgical condition can be simulated. Movement of the neck muscles often elicits slight stiffness. There may be ankle clonus and a Kernig and Babinski sign.

The *tongue* is swollen and moist early in the disease. In severe cases it becomes dry and coated, with a darkened border and prominent papillae. The tongue often protrudes from the mouth when profound

## CIRRHOSIS OF THE LIVER PRESENTING THE CLINICAL FEATURES OF XANTHOMATOUS BILIARY CIRRHOSIS, BUT WITH CONFIRMATION AT AUTOPSY

(Follow-up of Case Reported Previously\*)

F. W. HOFFBAUER, M.D., G. T. EVANS, M.D. AND C. J. WATSON, M.D.

In a series of cases of cirrhosis of the liver discussed by the present authors in the March 1945 issue of the *Medical Clinics of North America*, one case (Case III) was included which presented the clinical manifestations indicative of the diagnosis of xanthomatous biliary cirrhosis. In the interim since this report, this patient has come to autopsy, the findings of which were so instructive that it was believed they should be recorded as a supplement to the previous report. Reference to this report will reveal that this patient exhibited the characteristic hypercholesterolemia together with multiple xanthomas of the tendon sheaths, in addition to which there was chronic jaundice and manifest evidence of cirrhosis of the liver. Liver biopsy revealed a picture of an ordinary portal cirrhosis, and there was no evidence in the biopsy of intrahepatic xanthomas. As Thannhauser has emphasized, however, it is known that in xanthomatous biliary cirrhosis the obstructing xanthoma may be found only in the larger bile ducts. This patient died in coma exhibiting evidence of severe uremia, and with an obvious pericarditis. It was difficult to determine how much of the coma was due to hepatic insufficiency and how much to renal insufficiency. The blood urea nitrogen was 102 mg. per 100 cc. Shortly before death the serum bilirubin was 14 mg. per 100 cc.; the serum cholesterol was 375 mg. per 100 cc.; the cephalin cholesterol flocculation test remained 4+. The marked pruritus persisted until death.

The important findings at autopsy were as follows: (1) diffuse fibrinous pericarditis, (2) extensive diffuse hobnail type of cirrhosis of the liver, which weighed 1600 gm. The common duct was not dilated, but near the lower end of the duct a gallstone was found as noted in Figure 159. This was dark in color, and was found to consist almost entirely of calcium bilirubinate. Ether extraction failed to reveal any appreciable amount of cholesterol. Sections of the liver revealed an extensive diffuse portal cirrhosis of Laennec type (Fig. 160).

The anatomic findings in this case reveal that it is impossible to make the diagnosis of xanthomatous biliary cirrhosis with any degree of certainty, since in this case the blood chemical findings and the presence of xanthomas of the tendon sheaths were entirely characteristic and in fact strongly suggestive of the condition, yet at autopsy no evidence was obtained of xanthomas in the biliary tract. Nor was there any intrahepatic xanthomatous change such as described by Chvostek and believed by him to have been productive of cirrhosis. It is believed that the stone found in the common duct was a secondary phenomenon since, after seven years of jaundice, the common duct might have been expected to be dilated had the stone been the causative factor in the production of cirrhosis. The fact that the stone was largely composed of calcium bilirubinate and relatively little if any cholesterol suggests that it was simply due to inspissation of the bile, secondary to the reduced bile output of the cirrhotic liver.

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From the Department of Medicine and the Laboratory Service, University of Minnesota Hospital, Minneapolis, Minnesota.

\* Hoffbauer, F. W., Evans, G. T. and Watson, C. J.: Cirrhosis of the Liver: With Particular Reference to Correlation of Composite Liver Function Studies with Liver Biopsy. *M. CLIN. NORTH AMERICA*, 29(2):363-388 (March) 1945.

**Urine**—The urine may be highly colored. It is often strongly acid in reaction. There is an increased specific gravity. Old or debilitated individuals commonly show albumin in varying amounts, together with acetone bodies and microscopical alterations. Younger persons or those who have previously enjoyed good health do not manifest urinary changes so frequently.

**Cutaneous Biopsy**—Biopsy of skin lesions customarily reveals a perivascular inflammation and mononuclear cells containing rickettsiae.

### SUBSEQUENT COURSE

The subsequent course of Rocky Mountain spotted fever varies because manifestations of the disease are not constant in character and intensity. On one extreme are ambulatory patients and patients with abortive attacks and on the other patients with fulminating illnesses, with an early fatal termination. Most infections fall between the two extremes. In the usual case the acute phase lasts two or three weeks or longer. Temperature gradually recedes by lysis over a period of three to eight days. Although the patient is quite ill, convalescence with or without sequelae is finally established. It may take the individual weeks or months to recover completely. If the infection is fatal, death commonly occurs between the ninth and fifteenth day after onset from generalized toxemia, although it may take place later from complications.

The ambulatory patient has a mild temperature. The eruption is sparse. It may be scattered or localized in distribution. The afflicted individual is often not sufficiently ill to remain in bed. The illness has a duration of less than two weeks.

Abortive attacks show a sudden and stormy onset. The initial fever is high and the pulse full and bounding. The eruption is fleeting in character. Symptoms gradually or rapidly recede in severity, so that recovery is complete in several days to a week.

In fulminating infections death occurs three to five days after onset. The individual is stricken with toxemia so severe that the body defenses are literally overwhelmed. There is either no eruption or one in which the lesions rapidly coalesce and form large purpuric areas. The central nervous system shows early involvement. Exitus apparently ensues before the victim has had an opportunity to cope with the infection which has engulfed him.

### DIAGNOSIS

In the diagnosis of Rocky Mountain spotted fever there are several points which the attending physician must bear in mind. The disease occurs in the spring and summer months and strikes individuals residing in rural areas rather than in urban communities. The patient may give definite history of tick bite prior to becoming ill, or examination

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The test, if carefully done, will differentiate Rocky Mountain spotted fever from typhus fever in most instances. It becomes positive about the same time as the proteus agglutination test, but sustains its high titer for a longer period of time, perhaps even years.

The technic for the rickettsial agglutination test is likewise simple. To appropriate serum dilutions on hanging drop slides, formalin inactivated antigen, prepared from tissue cultures or yolk sacs of infected embryos, is added. Incubation is carried out at 40° C for four hours and the slides then refrigerated over night before a final reading is made. To the present, not enough is known regarding the time of appearance of rickettsial agglutinins and their persistence after recovery from tick fever. It is likely, however, that they last for a long time.

#### DIFFERENTIAL DIAGNOSIS

There is a possibility of confusion between Rocky Mountain spotted fever and other disease states, particularly when the illness is encountered in a region where its presence is not anticipated or when seen by those unfamiliar with its symptomatology. Typhoid fever, severe measles, scarlet fever, smallpox, chickenpox, purpura hemorrhagica, epidemic cerebrospinal meningitis, various septicemias, Colorado tick fever and endemic typhus fever are the most important of these. The majority of the entities with the exception of the last cannot be dealt with in this article.

Eruptions resultant from administration of the *sulfonamides* frequently cause diagnostic confusion. Evaluation of the history of onset, subsequent course, dosage and the drug used together with the general appearance and manner of spread are essential for the purpose of differentiation.

**Typhus Fever**—In the eastern and southern sections of the country, endemic typhus fever is obviously confused with Rocky Mountain spotted fever, for the reason that both diseases are found in the same localities. There is a striking clinical resemblance between the two rickettsial infections, at times making differentiation a most difficult procedure. Endemic typhus fever is transmitted primarily by infected rat fleas, Rocky Mountain spotted fever by infected ticks. Typhus fever appears for the most part during the later summer and fall and spotted fever of the eastern type during the summer and early fall. Endemic typhus fever is found among food handlers, the infected individuals being urban residents. Spotted fever occurs for the most part in those having rural contacts.

Even though the symptomatology is quite similar in both diseases, the general clinical features are quite intensified in Rocky Mountain spotted fever. The incubation period is shorter, the onset more explosive and severe. The temperature rises more rapidly. Although it

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toms and mental changes are more profound. Delirium is more often encountered, coma preceding a fatal outcome. Convalescence is more slowly established.

Routine laboratory procedures do not furnish much assistance in differentiating the two diseases, agglutination with proteus X strains tending to be positive at some time during the course of both. In order to establish absolute identification it may be necessary to study the effect of virus on laboratory animals. *Animal inoculations* and *cross immunity tests* are often used. Male guinea pigs and male white rats are given intraperitoneal injections of 5 cc. of whole blood taken from the infected individual. A heavy exudate with an abundance of rickettsiae in the scrotal sac of either animal is strong indication of endemic typhus fever. If the reaction occurs in the rat the evidence is conclusive. When the animals react mildly a final opinion can be given only by cross immunity tests following their recovery. The significance of the procedure depends upon the finding that animals which have recovered from Rocky Mountain spotted fever remain susceptible to typhus fever, and that animals which have recovered from typhus fever remain susceptible to spotted fever, but not to further inoculations of typhus fever virus.

The *complement-fixation* and *rickettsial agglutination tests* while relatively new procedures appear to be most effective ones for differentiating typhus fever from tick fever. Use of the specific antigens result in a positive reaction to typhus or spotted fever serums, as the case may be. The procedures are of additional importance because they retain their high titer for a period of months or years. They may be of utmost value in identifying or differentiating the two diseases when the infection to be diagnosed has occurred at some time in the not too distant past.

#### COMPLICATIONS AND SEQUELAE

Rocky Mountain spotted fever is a self-limited disease, terminating either in recovery within a few weeks time or in death during the height of the fever from toxemia or during the later stages from complications. Seriously ill patients are said never to recover if severe complications ensue. The usual ones are lobar or bronchopneumonia and phlebitis. Hiccup, splenitis and hemorrhages from the nose, intestines or kidneys take place. Less frequently seen are iritis, acute nephritis and hemiplegia.

Among the sequelae which can occur are neuritis, joint pains, deafness, visual disturbances, slurring of speech and mental confusional states. Degenerative processes in the aged may be accelerated by the illness. Some persons who have recovered from very severe infections seem to lack their former endurance for the remainder of their lives. In occasional instances mental acuity is definitely impaired.

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**Hygienic Measures**—Care to the skin is important. Equal parts of hamamelis water (witch hazel) and alcohol in water applied once or twice a day as a sponge often comforts and invigorates severely ill patients. It removes soreness from muscles and revives them. They are less mentally dulled, appearing stronger for several hours following the procedure. Mouth hygiene is important. Oral antiseptic washes, varied from time to time, rid the region of accumulated waste products, so that sufferers are made more comfortable during the acute phases of the disease.

**Convalescent Serums and Transfusions; Autohemotherapy**—Convalescent serums and transfusions have been resorted to, apparently without beneficial effect. Autohemotherapy has been used by some physicians, 10 to 20 cc of citrated blood from the patient being readministered intramuscularly. Although the action is an empirical one, beneficial results have been reported from its use. The procedure is repeated as often as necessary.

**Vaccines**—Tick vaccine must never be used for treatment. It has no beneficial action when used for this purpose. In milder cases its use is too drastic to be justified, in more severe ones it may prove dangerous as regards ultimate recovery.

**Antiserum**—Recently Topping has produced an immune serum in rabbits, using tick virus as the antigen. The rabbit serum has been shown to contain large amounts of antibodies. Satisfactory results have been achieved from its use, at first in animal experimentation and later in an increasing number of human beings. Though the results are not conclusive, mainly because of the relatively small series, they are sufficiently encouraging to warrant use of the serum. As in the case of other specific antisera, it must be administered as early as possible in the course of the disease, preferably before the fifth day of illness. There is no evidence that the serum is of any value if given later than the fifth or sixth day of fever. It is administered intramuscularly in divided doses, the total being approximately 1 cc per kilogram of body weight. The anti-Rocky Mountain spotted fever serum is now commercially available.

**Drugs**—Many drugs have from time to time been lauded as specifics in the treatment of Rocky Mountain spotted fever. It is agreed that the action of the majority of them is not certain and for that reason they have been generally discarded. Drugs of the *sulfonamide* series have little or no value in the management, according to present information. Experimental evidence would indicate that their action is harmful. If pneumonia, phlebitis or other complications due to secondary invaders appear, their use is certainly justified, the drugs of choice depending on the nature of the invading micro-organisms.

Over a period of the past ten years I have routinely used *neoparsphenamine in metaphen solution* as an adjunct to care in cases under

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to pass the hand occasionally over the back of the neck in order to detect crawling ticks. They may crawl up the outside of the clothing and gain access to the body by working themselves beneath the collar.

Clothing should be removed at least two or three times a day and the body thoroughly examined for the presence of crawling or attached ticks. As they hide away in body folds, crevices and hairy portions free from rubbing, a diligent search must be conducted. Persons must again inspect their persons, clothing and bedding before retiring for the night in the open. The precaution is most important when two persons sleep in close proximity. Infected ticks may attach themselves to both individuals successively. The first one may escape infection or be but mildly ill, the second one more seriously so from reactivation of virus in the tick vector by blood ingestion from the first victim.

Camps should be located where rodents are few, preferably in places where no low grass, sagebrush or small bushes are growing. Wooded areas along creek banks are best avoided as are the vicinities of old trails and roads. Ideal camping spots are usually where standing timber is present with a minimum of low vegetation.

While in tick-infested localities it is unwise to leave bedding spread on the ground during the day. It attracts ticks, often from a considerable distance. After return from trips, clothes and bedding should be carefully gone over, aired and then removed to buildings not used for human habitation. Once ticks have taken up their abode in a location, eradication is apt to prove most difficult and uncertain.

**Removal of Ticks and Treatment of the Bite**—When ticks gain access to body surfaces they move slowly about for a variable length of time, during which they seek suitable locations for attachment. The process is not noticeable to victims, nor are they usually aware of crawling ticks. Sources of minor irritation should always be investigated. It is supposed that vectors of the disease are not actively infectious until several hours have elapsed, but little reliance can be placed in this contention.

When located, attached ticks must be removed without delay. As a rule the head of the tick is embedded beneath the surface of the skin, the body remaining free and protruding at an angle from it. The head is held firmly in place by mouth parts, so that hasty or careless plucking often serves to remove the body alone, leaving the remainder in place to serve as a potential source of infection. Gentle traction may be successful in removing the tick. Close inspection then reveals it to be intact, often with a small fragment of epidermis caught in the mouth parts. Failing in the procedure, a small piece of epidermis in which the tick's head lies embedded must be elevated with a pair of tweezers and a tentlike wedge of tissue snipped with a fine pair of scissors. The point of a scalpel or hypodermic needle can be inserted beneath the tick's head and removal effected by turning the point up-

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from many parts of the body. Because of its multiple constituents, blood has naturally been used for many therapeutic indications. The present trend is toward the use of the specific component needed by the patient whenever it is available, rather than the administration of whole blood for all purposes, as was common practice until a few years ago. This is both more economical and more efficacious. In correcting deficiencies of particular components, two general types of therapy may be used—replacement or stimulation. *Replacement* consists in the passive transfer of the missing component from an outside source and is frequently a matter of urgent necessity. *Stimulation* consists in providing the stimulus to the manufacture of the missing component by the patient, with gradual but more lasting results if the patient is able to respond.

**Functional Components of Blood.**—Blood is a suspension of cellular elements in a fluid matrix, the plasma.

TABLE 1.—CELLULAR ELEMENTS OF THE BLOOD

Physiologic Data			Therapeutic Data		
Component	Source	Function	Replacement	Stimulation	Disease
Red blood cells	Bone marrow	Oxygen transport	Whole blood Resuspended cells	Liver extract Iron Vitamins B+C Thyroid	Hemorrhage Hemolytic anemia Aplastic, myelophthitic and azotemic anemia Pernicious anemia Hypochromic anemia Deficiency Hypothyroidism
Polymorphonuclear leukocytes	Bone marrow	Phagocytosis, defense against infection	(Whole blood)	(Crude liver extract) Stop offending drug or control infection	Agranulocytosis
Eosinophilic and basophilic leukocytes	Bone marrow	?	....	....	....
Lymphocytes	Lymph nodes	?	....	....	....
Monocytes	Tissues	Phagocytosis	....	....	....
Platelets	Megakaryocytes of bone marrow	Clot retraction	Fresh whole blood (Fresh Plasma)	Stop offending drug or control infection	Thrombocytopenic purpura

Parentheses denote treatment of doubtful value.

**Cellular Elements.**—From the clinical standpoint, three groups of cellular elements are important—the red blood cells, which normally constitute approximately 40 per cent of the total blood volume, the white blood cells, and the platelets. A brief summary of our knowledge of these components is given in Table I.

**Plasma Proteins.**—Sixty per cent of the total blood volume of a normal individual consists in plasma, an aqueous solution containing many solutes but principally sodium, chloride and bicarbonate ions, glucose, simple nitrogenous com-

- Rh factor, *Jan*, 232, 254  
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pounds, and proteins. It is the concentration of the latter (7 per cent) which chiefly distinguishes plasma from its filtrate, the interstitial fluid.

The plasma proteins are a large and diverse group of molecular species ranging from the relatively symmetrical albumin molecule, with its small size and high net charge giving it its osmotic potency, to the long rod-shaped fibrinogen molecule, specially suited to the formation of the tangled fibrillar structure of the clot. In recent years separation of these proteins into fractions in which specific functions are concentrated has been achieved<sup>1</sup> and these products of plasma fractionation, developed from blood collected by the American Red Cross for the armed forces, will undoubtedly find their way into civilian medicine in due time. The principal plasma proteins of importance to the physician have been recorded in Table 2.

*Water and Electrolytes.*—Neither the blood cells nor the plasma proteins would be of much use without water, which is the principal constituent of the body, comprising approximately 70 per cent of its weight. Body water is distributed between three "compartments"—(1) the cells, (2) the interstitial fluid and (3) the plasma—in accordance with complex osmotic equilibria which depend

TABLE 3.—BODY WATER

	Total Volume	Per Cent of Total Body Weight	Principal Cations	Principal Anions	Protein Conc.
Intracellular fluid	35 liters	50	K <sup>+</sup> , Ca <sup>++</sup> , Mg <sup>++</sup>	HPO <sub>4</sub> <sup>-</sup>	20-30%
Cell Walls					
Interstitial fluid (includes spinal fluid, aqueous humor)	10.5 liters	15	Na <sup>+</sup>	Cl <sup>-</sup> , HCO <sub>3</sub> <sup>-</sup>	.01-1 % (Lymph may run as high as 3-4%)
Capillary Walls					
Plasma	3.5 liters	5	Na <sup>+</sup>	Cl <sup>-</sup> , HCO <sub>3</sub> <sup>-</sup>	7%

Plasma and interstitial fluid = extracellular fluid.

upon the respective permeabilities of the different membranes separating the "compartments" (see Table 3).<sup>2</sup> From the practical standpoint, the volume of extracellular fluid is maintained by the kidney which regulates it by its control of the excretion of water and sodium ions; while the volume of plasma is maintained by the plasma proteins, principally albumin, since the capillary walls are largely impermeable to protein molecules although freely permeable to sodium and other ions and small molecules. In any consideration of replacement therapy, it is essential not to forget the importance of the three cardinal solutions for parenteral use—physiological saline for the replacement of extracellular fluid, glucose for the provision of water and calories, and sodium bicarbonate or lactate for the correction of acidosis. Restoration of kidney function is an essential feature of the treatment of shock, and this involves both the restoration of blood volume to provide an adequate renal circulation and the provision of sufficient fluid for excretion.

**Laboratory-Control of Replacement Therapy.**—The accurate, recognition and proper treatment of disturbances of the various functional





of blood volume is devised, we shall continue to labor under this handicap.

However, it is possible to obtain much valuable information on changes taking place in patients by the combination of a few relatively simple laboratory measurements and clinical observations, which should be routine procedures in any hospital caring for acutely ill patients, particularly surgical patients (see Table 4 and Fig. 161).

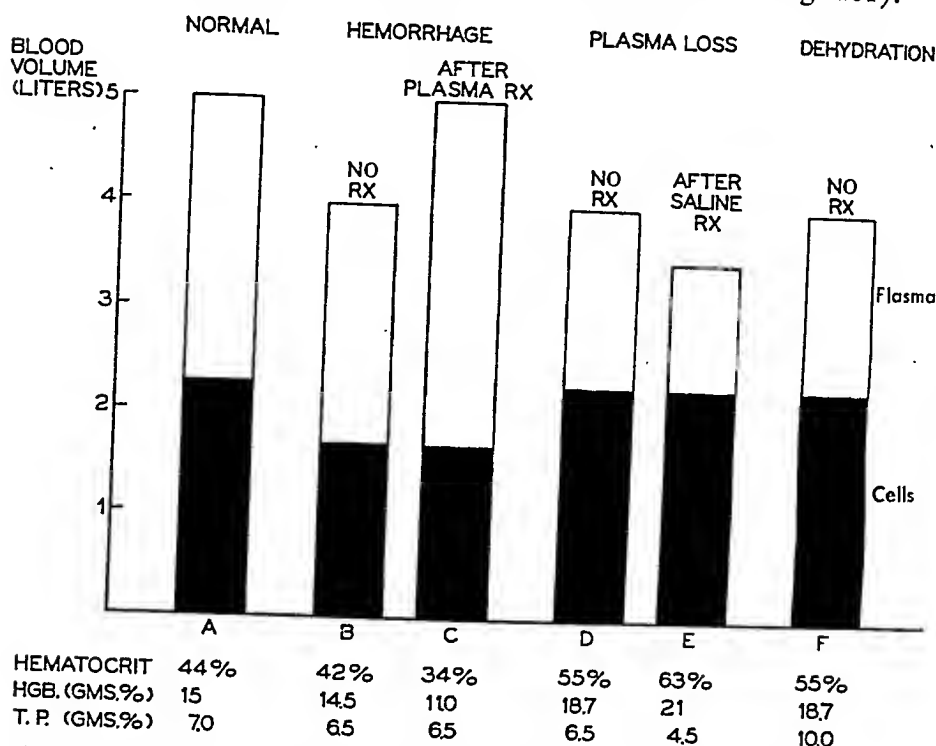


Fig. 161.—Schematic diagram of changes in blood volume and principal blood values after loss of body fluids. *A*, Normal; *B*, immediately after hemorrhage (note slight hemodilution); *C*, same after adequate replacement with plasma (note anemia); *D*, after plasma loss from burn (note hemoconcentration with normal plasma proteins); *E*, same after saline (note further fall in plasma volume and hypoproteinemia); *F*, dehydration (note hemoconcentration with high serum proteins).

Perhaps the most useful addition to the methods for following the progress of therapy in patients with shock or burns has been the introduction of simple methods for the determination of specific gravity of biological fluids. The so-called "falling drop" method has been used clinically for a number of years,<sup>3</sup> but recently a new method, making use of copper sulfate solutions, has been introduced.<sup>4</sup> By this method the specific gravity of whole blood, which is a relatively accurate measure of the hemoglobin concentration, and the specific gravity of the plasma, which is a good measure of the plasma protein concentration, can be determined with a very small sample of blood by any technician in a few minutes, the only equipment necessary being a few bottles of standardized copper sulfate solution and a centrifuge. These two values give the important data for



**TRANSFUSION FOR PLATELET DEFICIENCY.**—Thrombocytopenic purpura attended by significant hemorrhage, anemia or bleeding in a vital area constitutes an indication for transfusion. Since the platelets are rapidly destroyed when blood is stored, fresh blood should be used in these cases.

**TRANSFUSION FOR HEMORRHAGIC DISEASES.**—The value of various specific components in the therapeutic arrest of hemorrhage in hemophilia and bleeding due to hypoprothrombinemia is discussed later. Fresh whole blood may be used when plasma or specific fractions are not available in attempting to stop bleeding in hemophilia or hypoprothrombinemia.

**New Developments in Blood Transfusion.**—**IMPORTANCE OF THE RH FACTOR.**—It has been demonstrated<sup>8</sup> that about eighty-seven per cent of the general white population, irrespective of their blood groups, possess a factor (an agglutinin) in their red blood cells which has been called Rh. These individuals are referred to as being Rh-positive. The other 13 per cent who do not have this factor in their red blood cells are referred to as being Rh-negative. The Rh-negative individuals can form antibodies (anti-Rh agglutinins)<sup>9</sup> under two circumstances:

1. *When repeated transfusions of Rh-positive blood are given to Rh-negative individuals.* The first time such a transfusion is given there are no ill effects. However, the Rh-negative individual may become sensitized and begin to develop anti-Rh agglutinins. After repeated transfusions with Rh-positive blood, the titer of these agglutinins may become significant. Not all individuals will develop demonstrable anti-Rh under these conditions but the sensitized Rh-negative patient who does may suffer a hemolytic transfusion reaction on subsequent infusion of Rh-positive cells. Once such a reaction has occurred, all future Rh-positive transfusions are apt to produce increasing symptoms of hemolysis.

2. *When an Rh-negative woman bears repeated Rh-positive children, she may develop anti-Rh agglutinins.* Presumably this takes place because of a break in the placental barrier which allows Rh-positive cells from the fetus to enter the maternal circulation and sensitize her. Clinical manifestations of such isoimmunization usually do not appear in the first pregnancy of Rh-negative women unless they were previously sensitized by an Rh-positive blood transfusion. After the anti-Rh agglutinins have been formed by the mother they may be transmitted back to the fetus to produce hemolytic anemia of the newborn (erythroblastosis foetalis) in her subsequent Rh-positive offspring. Actually, this phenomenon is seen in only one out of fifteen matings in which the mother is Rh-negative and the father Rh-positive.

**Practical Applications.**—1. Whenever repeated transfusions are contemplated or a previous transfusion has been given, Rh typing should be done and only Rh-negative blood transfused into Rh-negative recipients.

## CONTRIBUTORS TO THIS NUMBER

Hugo L. Bair, MD, BS, Consulting Physician in Section on Ophthalmology<sup>1</sup>, Assistant Professor of Ophthalmology<sup>2</sup>

J Arnold Bargaen, MD, BS, MS in Medicine, FACP, Head of Section in Division of Medicine<sup>1</sup>, Associate Professor of Medicine<sup>2</sup>

Nelson W Barker, MD, BA, MS in Medicine, FACP, Consulting Physician in Division of Medicine<sup>1</sup>, Associate Professor of Medicine<sup>2</sup>

William H. Bickel, MD, BA, MS in Orthopedic Surgery, Consulting Surgeon in Section on Orthopedic Surgery<sup>1</sup>, Instructor in Orthopedic Surgery<sup>2</sup>

Alex E Brown, MD, BS, MS in Medicine, FACP, Consulting Physician in Division of Medicine<sup>1</sup>, Assistant Professor of Medicine<sup>2</sup>

Henry A Brown, MD, Consulting Physician in Section on Otolaryngology and Rhinology<sup>1</sup>

Louis A Brunsting, MD, MS in Dermatology and Syphilology, Consulting Physician in Section on Dermatology and Syphilology<sup>1</sup>, Associate Professor of Dermatology and Syphilology<sup>2</sup>

Haddon M Carryer, MD, BA, MS, Fellow in Medicine<sup>2</sup>

Edward N Cook, MD, BS, MS in Urology, Consulting Physician in Section on Urology<sup>1</sup>, Assistant Professor of Urology<sup>2</sup>

Philip D. Gelbach, MD, BS, First Assistant in Medicine<sup>1</sup>, Fellow in Medicine<sup>2</sup>

Melvin T. Gorsuch, MD, BA, First Assistant in Medicine<sup>1</sup>, Fellow in Medicine<sup>2</sup> On leave for military service since contributing

Ernest M Hammes, Jr, MD, BS, First Assistant in Neuropathology<sup>1</sup>, Fellow in Neurology and Psychiatry<sup>2</sup>

Malcolm M Hargraves, MD, BA, Consulting Physician in Division of Medicine<sup>1</sup>, Instructor in Medicine<sup>2</sup>

Frank J Heck, MD, BS, MS in Pathology, FACP, Head of Section in Division of Medicine<sup>1</sup>, Assistant Professor of Medicine<sup>2</sup>

<sup>1</sup> In the Mayo Clinic

<sup>2</sup> On the Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota

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**Practical Applications.**—1. Whenever repeated transfusions are contemplated or a previous transfusion has been given, Rh typing should be done and only Rh-negative blood transfused into Rh-negative recipients.

## CONTRIBUTORS TO THIS NUMBER

Edward H Ryneerson, M D , M A , M S in Medicine, F A C P , Consulting Physician in Division of Medicine<sup>1</sup>, Assistant Professor of Medicine<sup>2</sup>

Herbert W Schmidt, M D , B A , M S in Medicine, Consulting Physician in Division of Medicine<sup>1</sup>, Instructor in Medicine<sup>2</sup> On leave for military service since contributing

Charles H Slocumb, M D , B S , M S , Head of Section in Division of Medicine<sup>1</sup>, Assistant Professor of Medicine<sup>2</sup>

Harry L Smith, M D , M S in Medicine, F A C P , Consulting Physician in Division of Medicine<sup>1</sup>, Associate Professor of Medicine<sup>2</sup>

J M Stickney, M D , Ph D , M S in Medicine, Consulting Physician in Division of Medicine<sup>1</sup>, Instructor in Medicine<sup>2</sup>

William S Tinney, M D , B S , M S in Medicine, Consulting Physician in Division of Medicine<sup>1</sup>

Fredrick A Willius, M D , B S , M S in Medicine, F A C P , Head of Section in Division of Medicine<sup>1</sup>, Professor of Medicine<sup>2</sup>

<sup>1</sup> In the Mayo Clinic

<sup>2</sup> On the Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota

maining red cells.<sup>15, 16</sup> The use of these cells offers the advantage of the economy of using all the constituents of blood as well as providing a method of administering larger amounts of red blood cells with less of an increase in blood volume than if whole blood were used. The chief indications for its use are the anemias. It is of special value in anemia with cardiac insufficiency where it is desirable to add red cells without increasing the blood volume and hence increasing the load on the heart. It is also indicated when red cells are needed by any individual with a relatively normal blood volume. The use of resuspended red blood cells is contraindicated in shock, hemoconcentration, burns and hypoproteinemia, unless plasma or albumin are also administered to provide the needed plasma protein.

The method employed at the moment is to centrifuge the whole blood, remove the plasma and resuspend the red cells in pyrogen-free isotonic saline. This should be stored at 4° to 10° C. and discarded if any freezing occurs. Scrupulously sterile technic must be employed and if a purplish or black-red color or unusual odor appears the suspension must not be used. When once opened for use, any remaining suspension ought to be discarded. The suspension should not be warmed and must be filtered carefully before use, or administered through a suitable filter.

It is best to use these cells within twenty-four hours after bleeding as their life duration in saline suspension is short, although they have been used up to five days. If the cells are packed and resuspended in a relatively small amount of saline they are more fragile. The use of resuspended cells is probably only in its infancy. There is need for a more satisfactory diluent than saline so as to prolong the effective life of the cells to three to four weeks. Under these circumstances the suspension could be held long enough for the completion of sterility tests, and this would probably diminish the chances of transferring diseases such as malaria and syphilis, the agents of which die on storage in the cold for more than a few days.

**Blood Grouping Technic.**—Hemolytic transfusion reactions are almost always due to agglutination of the donor's cells by the recipient's plasma. With the increased use of group O blood, there has been a tendency to omit preliminary cross matching before transfusion since the donor cells are inagglutinable in any plasma. This practice is justifiable *provided the technic used for grouping the donors is above reproach*. In using A or B or AB cells where the donor's cells contain agglutinin, reactions may occur if there has been a mistake in grouping either donor or recipient and thus cross matching should always be done before transfusion. As has been pointed out above, Rh-negative blood or cells only must be used in certain situations. Table 5 shows the standard international blood group classification, which has properly replaced the Moss and Jansky classifications.

*Blood grouping serum must be of high potency and high avidity for*



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plasma. Plasma has the advantage that the red cells can be salvaged, and the separation between plasma and cells can be made promptly by centrifugation. Plasma may be salvaged from bank blood, which has been stored too long for use as such, but will have an appreciable content of hemoglobin and potassium and a low content of labile constituents such as prothrombin. Either plasma or serum should be pooled in lots derived from at least twelve donors. This lowers the isoagglutinin content markedly, and avoids the danger of destruction of the recipient's cells which might occur if a large dose of plasma with a high isoagglutinin titer for his cells were used. Pooled plasma can be given in large amounts without preliminary cross matching. Its sterility should be checked and serologic tests for syphilis made on the individual bloods before release for clinical use.

TABLE 6.—FORMS OF PLASMA AND SERUM

Form	Storage	Preparation for Use	Colloid Osmotic Pressure	Nutrition	Prothrombin	Fibrinogen	Hemophilic Globulin	Antibodies
Liquid Plasma Serum	Room temp. Sterility must be proved	None	+	+	0	0	0	0(1)
Frozen Plasma Serum	-10° C. for months	Thaw at 37° C.	+	+	+	+	+	0(1)
Dried Plasma Serum	Any natural temp. for year. Use in 2-3 hrs.	Reconstitute with water	+	+	+	+	+	+
			+	+	0	+	+	+
			+	+	0	+	+	+

(1) Antibodies preserved for a number of months if stored at ice box temperatures.

Plasma or serum can be stored for use in several forms. Since these forms differ in their content of various functionally important constituents, the physician should be familiar with the properties of each. These are listed in Table 6. In the administration of plasma or serum in any form, as with whole blood or resuspended cells, the inclusion of a suitable filter in the tubing through which the fluid is administered is imperative to exclude particulate matter.

Liquid plasma has the great advantage of being capable of storage without refrigeration and of being available for immediate administration to patients in shock, where speed is essential.<sup>19, 20</sup> It provides the needed colloid, but other functional constituents are lacking for the most part.<sup>21</sup> The labile components are best preserved in frozen plasma.<sup>22</sup> It must be thawed before use, which takes time. Dried plasma must be reconstituted before use, which requires several minutes and means that the package must contain a bottle of sterile pyrogen-free water as well as the bottle of dried plasma. It can be shipped and stored under almost any conditions with a fair degree of preservation

retina the concentrations approached those in the blood, while in the vitreous, aqueous and lens the concentrations were definitely lower. Paracentesis produced a decided increase of the concentrations in the aqueous, especially of sulfathiazole and sulfadiazine. Inflammatory conditions of the eyes and vasodilatation from the instillation of vasodilators in the conjunctival sac also produced increases of the intraocular concentrations.

A few analyses of eyes obtained at necropsy from patients who had been treated with sulfonamide compounds just prior to death have yielded results similar to those obtained in the experiments on animals.

Efficient dosage for eye infections is judged by the level of the drug in the blood stream. Thygeson<sup>7</sup> stated that this should be 5 to 10 mg in each 100 cc of blood when oral administration is employed. According to Bellows and Chinn<sup>8, 4</sup> traces of the drugs can be found in the eye within fifteen minutes. Maximal concentrations may occur in about six hours, except in the lens, in which the maximum may be reached only after about twelve hours.

The eye presents a relatively large area for absorption of locally administered sulfonamide compounds. Local administration, however, presents several aspects in relation to the action of the drugs. To be of real value, the drug must be absorbable in amounts sufficient to build up a therapeutic concentration in the affected tissues. The amount absorbed depends on the solubility of the drug, on the form in which it is applied and on the vehicle in which it is dissolved or dispersed. None of the sulfonamide compounds are very soluble in water. Moreover, aqueous solutions and suspensions are diluted and washed away by the tears too quickly for the attainment of high therapeutic concentrations of the drugs. Since the effect of the sulfonamide compounds is bacteriostatic and not directly bactericidal, the optimal concentration of the drug must be maintained at the site of the infection for a long time. Therefore the most efficient forms for topical administration are those which maintain a high concentration of the drug in contact with the conjunctival surfaces and in the locality of the infection. Emulsions, ointments and powders offer the best means of accomplishing this.

Thygeson and Braley<sup>8</sup> found that emulsions and jellies gave more rapid release of the drugs than did the ointments but were more irritating to the conjunctiva. The greatest persistence of the drug in contact with the conjunctiva and the least irritation were obtained when a hydrous wool fat-petrolatum base was used as a vehicle for the drug. Along the margins of the lids, however, where the preparation cannot be washed away readily by tears, the jellies and emulsions were considered to be more suitable than the ointment, since they were miscible

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amounts of fluid with salt or sodium lactate should be given by mouth as tolerated and supplemented by saline and glucose by vein as needed to maintain a good urine output. Excessive intravenous saline or glucose will produce a lowering of the plasma proteins and a return of the shock picture. Food should be given in as large amounts as can be tolerated in an effort to combat the wasting of body proteins. The diet should supply a liberal quantity of protein and calories and a generous supply of all the vitamins.

4. *The red cells.* Blood should be given frequently in an effort to sustain the hemoglobin level.

5. *Infection.* Infection of the traumatized area almost invariably occurs in burns as in war wounds and hence chemotherapy and local surgical treatment are of great importance.<sup>26</sup> Infection probably contributes markedly to the development of anemia and hypoproteinemia.

**SURGICAL SHOCK.**—The major component of surgical shock due to trauma or operation is hemorrhage. Whole blood is the treatment of choice, but plasma or albumin should be used to supply the colloid needed to maintain an adequate circulation while blood is being obtained for transfusion. In these cases, plasma or albumin restores the blood volume but the patient develops an anemia, which should be corrected as soon as possible to promote optimal recovery. Five hundred to 1500 cc. of plasma (or 25 to 75 gm. of albumin) are quite effective in these cases, but no more than 1500 cc. of plasma should be given without blood unless none of the latter is available. It is worth emphasizing that, in severe trauma, it is best to treat the patient promptly and if possible before clinical shock is evident.

**MEDICAL SHOCK.**—Peripheral vascular collapse, as manifested by low blood pressure, weak thready pulse, cold, clammy extremities, pallor, anxiety and restlessness, occurs in a wide variety of conditions. Its intelligent treatment demands recognition of the causative factors.

Where cardiac disease—acute myocardial failure after a coronary occlusion or cardiac tamponade developing from acute pericarditis—is the chief factor, therapy must be directed at the heart. Where metabolic disorders are the chief cause—the hypoglycemia of insulin shock or hypoadrenalism, the loss of electrolytes characteristic of diabetic coma or Addison's disease—not only is repair of the chemical deficit required (glucose or sodium chloride) but also replacement with the proper hormone. It is in severe infections such as scarlet fever, meningococcus meningitis, typhus fever and ulcerative colitis that the picture of shock is most often seen. Here multiple factors may be operative: (1) reduction in blood volume from loss of plasma through damaged capillaries or from loss of electrolytes by vomiting, diarrhea or sweating; (2) increase in capacity of the vascular system from loss of vasomotor tone; (3) hypoproteinemia; (4) anoxia; (5) hyperpyrexia; and (6) acute adrenal insufficiency as a result of massive hemorrhage into the adrenal glands in the rare instance of Waterhouse-Friderichsen syndrome. Control of the infectious process by intensive

the treatment of corneal infections and conjunctivitis as in the treatment of intra-ocular infection. In hyperemic, well-vascularized tissues, such as the inflamed conjunctiva, the concentration of the drug due only to topical administration would be expected to suffer a tendency to rapid decrease as a result of absorption into the blood stream. The increase of penetration caused by wetting agents should therefore aid materially in building up and maintaining an adequate concentration in these tissues. Although vasodilatation is of aid in building up the tissue concentration when the drug is given orally and brought to the site of the infection by the blood stream, it obviously is detrimental to maintaining effective concentration when topical administration is employed. For this reason, in the latter instance, it would be logical to employ vasoconstrictors along with the locally administered drug and wetting agent. Experimental work on this aspect of the problem as it relates to the concentration of drug in the conjunctival tissues has been neglected.

#### INFECTIONS FOR WHICH SULFONAMIDE COMPOUNDS ARE INDICATED

There are a number of infections of the eye and the ocular adnexae for which the use of the sulfonamide compounds is definitely indicated. In addition there are a number of other infections in which these drugs, although apparently inadequate by themselves to effect a cure, have been reported to be beneficial adjuncts to other forms of treatment. Outstanding therapeutic success with the use of sulfonamide compounds in ophthalmologic practice has been demonstrated in the treatment of trachoma, inclusion conjunctivitis, gonorrheal conjunctivitis and, as was to be expected, beta hemolytic streptococcal infections.

**Trachoma**—In the treatment of trachoma, apparently all of the commonly used sulfonamide compounds are effective when given orally. I have employed *sulfamerazine* recently in two cases of trachoma, one a fresh case, the other a case of old, previously inadequately treated trachoma in the third stage of the disease. In both cases the response to the orally given *sulfamerazine* was good, the inflammatory signs subsiding markedly after three to four days of the treatment. Local administration of sulfonamide compounds in the treatment of trachoma has not proved to be of much, if any, value. With oral administration, the dose need not be as high as in the case of most other diseases, but the treatment must be continued for a number of weeks, from three to seven. Occasionally, repeated courses of a few weeks at a time may be necessary to effect a cure of the active disease. Thygeson<sup>7</sup> considered it advisable to maintain a blood level of at least 3 mg. in each 100

eats a relatively small amount of protein in relation to the total caloric intake, hypoproteinemia develops more rapidly.

2. Excessive Protein Loss.—*Loss of protein from the body* occurs in the urine in the nephrotic syndrome, in the fluids removed by paracentesis of rapidly recurring effusions in the serous cavities and in the oozing of plasma from burns, wounds, or skin lesions such as eczema.

*Increased destruction of body proteins* occurs in infections, burns, and after operations or injuries when the catabolic activities may be so greatly enhanced that it is almost impossible to achieve nitrogen balance with any but enormous amounts of protein. As our methods for the treatment of serious infections and burns improve, the nutritional requirements of convalescence assume increasing importance.<sup>29</sup>

3. Defects of Protein Metabolism.—*Poor absorption* may be responsible. In certain gastrointestinal diseases such as pancreatic insufficiency or diarrheal disease the amount of hydrolyzed protein absorbed from the bowel may be diminished because of lack of proper enzymes or too rapid passage through the gut. The administration of hydrolyzed protein (amino acids) by mouth makes it possible to obtain a positive nitrogen balance in many of these cases.<sup>30</sup>

*Impaired synthesis* is sometimes present. In hepatic disease the organ which manufactures serum albumin is involved. Thus a low serum albumin level may be one of the signs of hepatic failure and is observed in cases of acute hepatitis and particularly in cirrhosis of the liver.<sup>31</sup>

CORRECTION OF HYPOPROTEINEMIA.—In the treatment of hypoproteinemia, the administration of very much larger amounts of protein is necessary than would be expected on the basis of the deficit in total circulating protein. Most of the administered protein is apparently stored in the tissues. In hypoalbuminemic dogs fed a very high protein diet, Elman<sup>32</sup> has shown that only one-thirtieth of the protein fed could be accounted for by the increase of circulating albumin. Obviously the correction of hypoproteinemia can be most economically achieved by stimulation therapy—namely, a high protein, high caloric diet, sometimes supplemented by amino acids and glucose administered either parenterally or orally. Unfortunately this takes time and the situation may demand rapid correction. Moreover, in the face of the increased breakdown of body protein occurring in infections and after injuries or in hepatic failure this may be ineffectual. Thus parenteral protein feeding has to be used frequently and plasma must be given by slow drip in doses of from 500 to 1000 cc. per day. If used, it should be supplemented in a patient who cannot take oral feeding by as many calories in the form of glucose as possible, and by injection of sufficient doses of vitamin B complex and vitamin C to insure good carbohydrate utilization; in the patient who can eat, a very large intake of protein with carbohydrate will increase the effectiveness of the injected plasma by sparing the body proteins.

ably the most frequent form of this infection is orbital cellulitis or infection of the lids. The skin of the lids is usually affected in erysipelas. Streptococcic conjunctivitis is comparatively rare, especially the type due to beta hemolytic streptococci. Panophthalmitis due to these organisms may occur after penetrating injuries of the eyeball. In all types, essentially the same degree of success is obtained with sulfonamide therapy as in cases of infection with these organisms elsewhere in the body. Penetrating corneal ulcer and panophthalmitis due to hemolytic streptococci would theoretically be the most likely to show much resistance to the treatment owing to the avascularity of the infected tissues. In such cases, it would be logical to combine local and oral therapy, using wetting agents also with the former.

**Other Infections**—Infection of the eye with the virus of *lymphogranuloma venereum* is rare. A few cases of conjunctivitis due to this cause have been reported as successfully or favorably treated with sulfonamide compounds.

In cases of *pneumococcic infection* of the eye, variable results have been reported. In many cases the infection has responded to sulfonamide therapy alone, but frequently such therapy had to be supplemented with other forms of treatment. The common forms of pneumococcic infection of the eye are conjunctivitis, corneal ulcer and panophthalmitis, usually following penetrating injury. Sulfapyridine has been the drug of choice for these infections and has been employed orally and topically. With pneumococcic ulcer of the cornea and with panophthalmitis it is advisable, to administer the drug by mouth as well as topically. If no early improvement is noted, or if the infection seems very severe, supplementary treatment should be used. I have treated one patient suffering from pneumococcic panophthalmitis successfully with sulfathiazole given orally and also locally as the powder, this treatment being used as an adjunct to daily drainage through the corneal wound.

Corneal ulcer and panophthalmitis due to *infection with Pseudomonas aeruginosa* have been reported as successfully treated with sulfonamide compounds when the treatment was started early. Such infections are severe and fulminating and, if not controlled at an early stage, frequently cause loss of the eye. It is advisable, therefore, to use the drugs both locally with wetting agents or iontophoresis and orally in order to obtain as rapid action as possible.

*Staphylococcic infections* are generally resistant to the usual doses of the sulfonamide compounds. Some favorable results in treating staphylococcic conjunctivitis, marginal blepharitis, impetigo of the lids and corneal ulcers, however, have been reported with topical appli-

## IV. USE OF PRODUCTS OF PLASMA FRACTIONATION

It is suggested from the above discussion that since whole blood and plasma have specific indications for therapy in a wide variety of conditions, the individual components would be even more valuable in isolated form. The products of plasma fractionation<sup>35</sup> have been given considerable clinical trial, but so far have been available only to the armed forces, except for immune serum globulin.

**Human Serum Albumin.**—This is distributed in 100 cc. bottles containing 25 gm. of albumin which is equivalent in osmotic effect to 500 cc. of citrated plasma. Albumin solution has contained in the past approximately twice the isotonic concentration of sodium chloride, but interest in its use as a physiological diuretic agent has led to the development of a solution of much lower salt content.<sup>36</sup> Besides the great conveniences of a small compact package, ready for use without reconstitution or cross matching, and the safety and ease with which it can be administered, albumin has the great advantage that it can be combined in any desired concentration with any of the solutions used parenterally. Five per cent albumin in saline solution is approximately isotonic with plasma and can be used interchangeably with it in the treatment of burns.

Indications for the use of albumin are as follows:

**Shock.**—Albumin provides effective colloid osmotic pressure for the emergency treatment of traumatic shock. It increases blood volume by drawing water from the tissues into the circulation, and in severely dehydrated patients additional saline should be provided for the relief of dehydration.

**Hypoproteinemia.**—In this condition it is the logical solution for replacement therapy, since it provides the maximum amount of protein with a minimum amount of fluid and no extra salt. Thus, rapid increase in the colloid osmotic pressure with mobilization of water from the edematous tissues can be achieved, by the injection of small amounts of material, a particular advantage in pediatric practice. The low salt content of the solution is of importance in the treatment of edematous patients with renal disease.<sup>37</sup>

**Proteins Concerned in Blood Coagulation and Their Derivatives.**—The formation of a blood clot is the result of a complicated series of chemical reactions. Since we can now isolate some of the substances involved in this mechanism, however, it is possible to "arrest" the process at various stages and use the intermediate products. Thus, prothrombin can be combined with thromboplastin for the formation of thrombin. If this is done quantitatively with a known amount of thromboplastin and a blood of unknown prothrombin content, the concentration of the latter can be determined by the length of time it takes the clot to form—the "prothrombin time." Thrombin itself has found many uses, particularly in the field of surgery. Combined with fibrinogen, it



oral sulfonamide therapy. Untoward effects from local treatment are chiefly local tissue irritations and adverse effects on tissue reparative processes. As Bellows<sup>2</sup> has demonstrated, the sulfonamide compounds when applied locally tend to prolong the healing time of wounds and to promote the formation of scar tissue. They have an unfavorable effect on actively growing epithelium and prolong about twofold the regeneration time of the corneal epithelium. Apparently the deleterious effect is primarily on young cells so that this effect should not be considered as a contraindication to their use on normal unbroken cornea. It does, however, make it advisable not to use these drugs any longer than necessary to combat infection when the corneal surface has been broken either by trauma or by ulceration.

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*bulin* prepared from human placenta since it is more potent, better standardized, and gives rise to very few reactions.<sup>38</sup>

The prophylactic use of gamma globulin has been proved for two diseases—measles and infectious hepatitis (epidemic "catarrhal" jaundice).<sup>39</sup> The results of available studies on its use are tabulated below:

Disease	Given after Exposure, before Symptoms Appear		Treatment after Symptoms Appear
	Prevention	Modification	
Measles	+ (Dose 0.1 cc. per lb. in first 6 days)	+ (Dose 0.025 cc. per lb. in first 6 days)	Some effect if given in large dose before rash appears
Infectious hepatitis	+ (Dose 0.1 cc. per lb.)	Under investigation	Under investigation
Mumps	0	0	0
Chickenpox	0	0	—

Key: +, proved effective.  
0, proved ineffective.  
—, no studies made.

The globulin is injected intramuscularly and in the usual doses causes very little or no local reaction and only rarely mild general symptoms, principally slight fever. It should not be used intravenously. Its most important civilian use is in the prevention of measles after exposure in sick or debilitated children or in the attenuation of the disease in healthy susceptible contacts. The mild disease carries a much lower risk of complications and probably gives rise to permanent immunity, though this has not been proved. Such passive immunization is effective for about three weeks and must be repeated after that interval if the patient is reexposed. Recognition of the mild disease may not always be easy. Fever, malaise and catarrhal symptoms are usually markedly diminished in intensity and duration. The rash may be sparse and transient. The incubation period may appear to be prolonged since the prodromal stage is largely eliminated.

#### V. REACTIONS FOLLOWING INTRAVENOUS ADMINISTRATION OF BLOOD OR ITS DERIVATIVES

The intravenous administration of whole blood, resuspended red blood cells, plasma, or albumin, while relatively safe, may at times be associated with reactions of different types and varying severity. No preparation of gamma globulin suitable for intravenous use has as yet

the only true indication of adequate dosage and should be determined as often as is necessary to be sure the patient is getting enough of the drug and that the concentration in the blood is maintained steadily. In an average infection in which sulfadiazine is given by mouth and is tolerated well, determination of the concentration of sulfadiazine in the blood every day or every other day may be sufficient. If an intracranial complication is present and there is vomiting, or if the drug is being given intravenously or subcutaneously as well as by mouth, it may be necessary to examine the blood for sulfadiazine as frequently as twice daily in order to be certain that a sufficiently high concentration of the drug is being evenly maintained.

It is our practice to estimate the twenty-four hour requirement of sulfadiazine for adults on a basis of 1 grain (0.065 gm) per pound of body weight. A third to a half of the total is given by mouth as an initial dose, and the balance is administered by mouth in equally divided portions, along with 10 grains (0.65 gm) of sodium bicarbonate. The concentration of sulfadiazine in the blood is determined six to eight hours after the initial dose and necessary adjustments in the dosage are made. For children a somewhat larger dose is necessary to obtain the desired concentration, usually  $1\frac{1}{2}$  grain (0.1 gm) per pound of body weight being required. In an average infection, such as acute tonsillitis or acute otitis media, a concentration of 8 to 12 mg of sulfadiazine per 100 cc of blood is usually adequate. If the infection is severe or if an intracranial complication is present, a concentration of from 15 to 25 mg of sulfadiazine per 100 cc of blood should be maintained. In the presence of an intracranial complication it is imperative that a high level of sulfadiazine be attained in the blood immediately. For this reason it is well to give a large initial dose of the drug intravenously. For an adult 100 cc of 5 per cent solution of sodium sulfadiazine in physiologic saline solution usually seems indicated along with the estimated oral dose of sulfadiazine. If the drug is not tolerated by mouth, intravenous administration is carried out every eight hours.

*Sulfamerazine* offers considerable promise in the treatment of infections of the ear, nose and throat but as yet it has not been given sufficient trial to warrant any definite conclusions.

**Acute Upper Respiratory Infections**—Few uncomplicated upper respiratory infections entail as much risk as treatment with a sulfonamide compound does. The drug is not effective against the virus of the common cold and in most cases the body's defense mechanism combined with the usual measures is able to combat secondary bacterial invaders. It would seem that treatment with sulfonamide compounds

those of the disease imparted. Treatment should be directed towards screening out diseased donors by a careful history, physical examination and routine serology. The problem of the transmission of homologous serum jaundice has received a great deal of attention recently,<sup>40</sup> but so far no satisfactory method of dealing with this problem has been devised. Recipients of icterogenic blood or plasma usually develop jaundice two to six months after receiving the transfusion, and the resulting hepatitis may vary from a severe and even fatal disease to one in which symptoms would not be recognized as of hepatic origin without laboratory studies.<sup>41</sup>

**Hemolytic Reactions (Due to Blood Incompatibility).—**These reactions, since they are usually due either to mismatching or Rh incompatibilities, are seen only with the use of whole blood, resuspended red cells, or nonpooled plasma. The reaction most often occurs after a relatively small amount of blood is injected but may at times be delayed until after a full transfusion depending on the strength of the agglutinin and its speed of action. It is wise to avoid transfusing anesthetized individuals, whenever possible, for fear of masking such a reaction. The recipient who is experiencing such a hemolytic transfusion reaction becomes restless and anxious. He often complains of pain especially over the kidney regions. This pain at times is excruciating. Chills and fever, dyspnea, vomiting and collapse may soon follow. Hemoglobi-nuria, oliguria and even anuria are fairly common. Later icterus appears with anemia. Uremia may be present if renal shutdown is prolonged.

Again the best prophylaxis is careful blood grouping and cross matching as discussed previously. Specific therapy is directed towards:

1. Alkalinizing the urine in an effort to free any acid hematin precipitated in the kidney and establishing a flow of urine in oliguric or anuric individuals. The measures commonly employed include intravenous one-sixth molar sodium lactate in doses of 500 to 1000 cc. in adults and 10 cc./lb. of body weight in infants and children, intravenous sodium bicarbonate either as an isotonic solution (1.5 per cent) or hypertonic solutions of 3 to 6 per cent. The oral administration of sodium bicarbonate requires dosages of 15 gm. per day in adults with the obvious drawbacks of the slow action of oral doses and the difficulty of vomiting when such high doses are employed.

If oliguria is marked or anuria is present, the decision as to the amounts and types of fluids to be administered should be guided by chemical and clinical observations. An attempt should be made to provide sufficient fluid to keep water available for excretion but not to flood the patient with water in such quantities as to seriously lower the concentrations of electrolytes in extracellular fluid.

2. Correcting the resulting anemia by the transfusion of fresh compatible blood.

3. Maintaining the patient with general supportive therapy.

from a possible toxic reaction, than if other measures alone were depended on to combat the acute mastoiditis. Vigorous well-controlled treatment with a sulfonamide compound should be instituted and administration continued in reduced doses for a week after symptoms have subsided.

Williams, and others,<sup>21</sup> Kopetsky,<sup>13</sup> Morrison,<sup>16</sup> Flake and Carey,<sup>9</sup> Cone,<sup>3</sup> Fenton<sup>8</sup> and Cirillo<sup>2</sup> have pointed out that treatment with sulfonamide drugs, particularly inadequate or poorly controlled treatment, may mask symptoms indicative of the true status of acute mastoiditis, or may so cloud the clinical picture that a threatened or present extension to the blood stream or intracranial extension may not be suspected. Williams<sup>20</sup> stated that this masking effect is becoming a much less serious problem as otologists learn to evaluate the influence which sulfonamide drugs may have on the symptoms and signs of disease of the middle ear and mastoid process.

Nitti and Bovet<sup>17</sup> demonstrated that mice recovering from streptococcic infections were susceptible to new infections with the same organism. This observation indicates that immunity to an infection does not develop when the infection is terminated by chemotherapy. It also tends to explain why an infection such as a peritonsillar cellulitis or acute otitis media may flare up quickly after the premature cessation of chemotherapy and third it indicates that the sulfonamide should be continued, in reduced doses, for several days after the infection is apparently under control.

Maybaum, Snyder, and Coleman<sup>18</sup> observed that treatment with sulfanilamide was ineffective in the presence of a suppurative focus in the mastoid process. Kopetsky<sup>13</sup> stated that although sulfanilamide will kill hemolytic streptococci in body fluids, it did not seem to exert the same influence when the organisms were lodged in an active osseous lesion. Eagleton<sup>5</sup> observed that sulfanilamide is not effective against organisms in encapsulated abscesses or in necrotic tissues.

Houser<sup>12</sup> felt that after central necrosis had occurred it was impossible to influence the abscess already formed. He felt that the drug no longer reached the region in question.

It seems to be the consensus that if one of the sulfonamide compounds is to be used in acute otitis media and mastoiditis, it should be used early and in adequate doses in the stage before the bone is involved. If great improvement is not manifest in three or four days, doses should be discontinued so that the symptoms and signs are not masked.

#### THE LOCAL USE OF SULFONAMIDES

With the sulfonamide compounds steadily increasing in importance as agents for combating bacterial disease, it was inevitable that local

the plasma proteins from the circulation and also is slowly deposited in the liver, thus interfering with protein synthesis and ultimately defeating its own ends.

*Pectin* has also been proposed and would appear to suffer from the defects of acacia but very little is known about its ultimate fate.

This list could be expanded considerably. So far no blood substitute which fulfills the criteria for a satisfactory therapeutic agent has been discovered, and as long as there is an adequate supply of human blood, plasma and plasma protein fractions, it will be surprising if any substitute can be found to do the job as well as the molecules developed by the process of evolution.

## VII. SUMMARY

An attempt has been made to summarize the basic knowledge in a very large field of therapeutics. No physician or surgeon can afford not to understand the fundamental principles underlying the proper use of blood, its various derivatives, and the common intravenous solutions. If this clinic has helped to clarify some of these principles and to indicate some of the therapeutic possibilities arising from the separation of blood into its component parts, it will have achieved its objective.

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a hydrogen ion concentration which was compatible with normal nasal activities. These authors recommended that a spray or drops of the neutral solution be used every two or three hours in acute upper respiratory infections. In subacute or chronic infections Proetz displacement was advised. Acute and chronic maxillary sinusitis were treated by irrigation through the natural ostium with a Pierce cannula and by instillation of a 5 per cent solution of microcrystals of sulfathiazole. Studies of the concentration in the blood of the sulfonamide drug employed revealed it to be uniformly low.

Ebert<sup>6</sup> reported having treated acute rhinitis in ninety-two cases by insufflation of sulfathiazole powder, they felt that the response was favorable.

Furstenberg,<sup>10</sup> who has routinely used sulfanilamide powder in simple and radical mastoidectomy wounds, stated that healing is more rapid with fewer stitch abscesses and less discomfort to the patient. In his opinion exuberant granulation tissue in radical cavities is less common when sulfanilamide powder is employed and epithelization has a better chance to progress satisfactorily.

Guerry and Putney<sup>11</sup> used a gauze impregnated with a paste of sulfathiazole and sterile water to pack simple mastoidectomy wounds. They reported a shortening of the period of drainage by 52.8 per cent and shortening of the hospitalization time by 55 per cent in their series of cases.

Marks<sup>14</sup> reported ten cases of chronic maxillary sinusitis in which 20 and 50 per cent suspensions of sulfathiazole in a lubricating jelly (K-yor luzo) were injected two or three times weekly following antrum puncture and lavage with physiologic saline solution. They found the medication effective in 70 per cent of their cases, the average time for resolutions being three to four weeks.

Fabricant<sup>7</sup> stated that the effect of a nasal medicament on the mucous membrane of the nose and sinuses and its relationship to ciliary action and in nasal hydrogen ion concentration must always be considered. He concluded that some of the sulfonamides now used locally are not compatible with these important factors in nasal physiology. He was of the opinion that some locally applied sulfonamides may produce even more irritation of the mucous membrane than usual in the presence of the transitory anoxia produced by an accompanying vasoconstrictor. Fabricant also emphasized that patients who have used sulfonamide drugs locally are subject to all the risks entailed by oral or parenteral administration.

In the light of present knowledge it would seem that local application of the sulfonamide compounds in inflammatory diseases of the

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# COMMON PROBLEMS IN MANAGEMENT OF PNEUMONIA

H CORWIN HINSHAW

THE medical literature of recent years is richly supplied with authoritative information on practical and theoretic aspects of sulfonamide treatment of pneumonia. The choice of drugs, the methods of administration and information concerning toxic manifestations of these drugs are well described in several publications which have been widely read and are extensively followed. It should be our aim, not to emphasize these well-known principles further or to suggest any important amendments to them, but rather to review some of the common problems which the attending physician must solve when utilizing sulfonamide preparations in the treatment of pneumonia. It would also be of interest to note trends of investigation which may indicate what further developments may occur.

## TRENDS OF INVESTIGATION

The therapeutic advances in treatment of pneumonia made during recent years have been unparalleled but there is no evidence that progress has ceased. It seems more probable that advances will continue at their present rapid rate toward the goal of an ideal therapeutic procedure. Preliminary reports suggest that antibiotics, such as penicillin, may represent the closest approach to an ideal therapeutic agent yet to be revealed. When the chemical composition of such preparations has been determined, the way may be opened to the synthetic production of many compounds of new chemical groups with ever-increasing advantages. A substance which will control bacterial infection rapidly and effectively without harm or inconvenience to the host would have appeared totally impracticable only a few years ago, but today it appears well within the range of practical attainment. These chemotherapeutic agents have such a profound effect upon the basic metabolism of bacteria of many divergent species that it seems quite possible that eventually all types of bacterial disease may yield to this fundamental approach. Even at this time there are few important bacterial diseases not affected in greater or less measure by preparations of the sulfonamide group. Drugs of the diaminodiphenylsulfone group attack still other organisms. The development of a still different group of compounds related to penicillin may be accomplished and these compounds may deal effectively with many of the remaining types of bacterial infection.

layman may be excused for heeding this propaganda, but not the physician. He has his medical education which should have taught him to consult recent approved textbooks—the United States Pharmacopoeia, the National Formulary, the publications of the American Medical Association and the American Pharmaceutical Association, and lastly the advice of the Council of Pharmacy and Chemistry in dermatology and syphilology, either directly or through its annual volume of New and Nonofficial Remedies. A sufficient knowledge of drugs advocated by experienced dermatologists is necessary, and their indications and contraindications, as well as the proper methods of application, should be known. Printed instructions are of great value, and the physician should know the necessary amount to be used and prescribe neither too much nor too little. An ounce of an ointment is sufficient for only one application to the average adult body.

**Psychic Factors.**—Before prescribing any medication one must evaluate the psychic reaction of the patient to the rebellious outburst of the skin. There is nothing more disturbing to the average individual than an unexpected or recalcitrant disfigurement or disturbance of the skin. The diagnosis, the prognosis and the possible effects of medication must be explained to the patient. No disease should be pronounced incurable unless an unquestionable diagnosis is made of an entity which has been proved to resist all therapy. I have seen cases of psoriasis that did not recur for fifteen or more years. Cases misdiagnosed by more than one experienced observer as pemphigus have healed and remained well. There is a great psychic factor in the background of many cutaneous diseases. It alone may be the cause of pruritus, urticaria, angioneurotic edema, dermatitis factitia, phobias, hyperhidrosis, pompholyx, and changes or loss of hair. In my experience, psychic traumas have caused exacerbations of neurodermatitis, lichen planus and psoriasis. I have seen all three greatly improved by psychosomatic therapy, after proper dermatologic therapy alone had failed. A certain amount of psychotherapy is of value in all types of dermatologic patients. Even a man with a small benign basal cell epithelioma may develop a phobia unless he is assured that this lesion can be cured. Therefore, the first step in therapy should be reassurance, not a defeatist attitude of "try this and see what happens." A knowledge of drugs and their actions will give confidence to the physician which he in turn will impart to his patient. The following briefly summarizes these remedies.

#### TOPICAL APPLICATIONS

**Baths.**—Baths have a definite value in cleansing and soothing the skin. Since soap is contraindicated, corn starch or a combination of oatmeal and sodium bicarbonate—the so-called *colloid bath*—should be used. The water should not be hot, rather about 98° F.

**Wet Dressings.**—There is nothing more soothing to an acutely in-

ence of many physicians. It is true that some physicians have found doses much smaller than those usually recommended to be reasonably adequate for many infections and, in consequence, have evolved practices that, however adequate they may be to deal with mild infections, are inadequate to deal with more severe infections.

To many physicians the determination of the concentration of sulfonamide drugs in the blood stream appears to be an unnecessary refinement for average patients who are responding properly to treatment. All will agree that the most important indication for studies of the concentration of sulfonamide compounds in the blood is in the case of the patient who is not responding to therapy in the anticipated manner. In such instances treatment should not be discontinued until the concentration of sulfonamide compounds in the blood has been determined to exclude the possibility that either inadequate absorption or inadequate dosage is responsible for the failure of the drug. Under these circumstances, parenteral administration may offer a rapid, satisfactory solution to a perplexing problem.

#### DIAGNOSTIC PROBLEMS

Most difficult diagnostic and therapeutic problems arise during the course of epidemics of febrile respiratory diseases, such as influenza. Not only must the physician be on guard to detect complicating secondary bronchopneumonia at such times, he must also realize that cases of primary pneumonia of conventional type do occur independent of influenza epidemics.

Not only primary pneumonia but other respiratory diseases, including the acute exacerbations of symptoms in such chronic diseases as tuberculosis, bronchiogenic carcinoma, pulmonary abscess and so forth, may resemble influenza. Every epidemic of influenza yields an increased number of cases of such chronic diseases in which diagnosis has been unfortunately but often unavoidably delayed. The only apparent solution of the problem would depend upon the physician's warning his patients that continued contact should be maintained between physician and patient until an obvious state of normal health is regained. This routine practice might prevent repetition of instances in which early symptoms of pulmonary tuberculosis or other chronic disease of the lungs have been confused with epidemic influenza, or indeed in which the symptoms may have been those of epidemic influenza which rekindled a former latent symptomless disease. It seems probable that acute epidemic diseases of the respiratory tract may lead to serious exacerbations of such diseases as tuberculosis and that spon-

tity of alcohol before being incorporated into the lotion. The pharmacist realizes this necessity and may be depended upon to carry out the procedure without specific instructions to do so. Goodman<sup>3</sup> suggests a formula for suspension of colored zinc oxide (calamine or neocalamine):

Stearic Acid .....	4.0
Triethanolamine .....	1.0
Distilled water .....	q.s. ad 100.0
To which add	
(a) Prepared Calamine .....	8.0
Zinc Oxide .....	8.0
or (b) Prepared Neocalamine .....	15.0
or (c) Prepared Neocalamine .....	8.0
Zinc Oxide .....	4.0

Many useful formulas, such as the following,<sup>4</sup> may be prepared using bentonite:

Bismuth Subcarbonate .....	25.0
Bentonite, 6%, in Lime Water .....	ad 120.0
Zinc Oxide .....	6.0
Talc .....	6.0
Sodium Borate .....	6.0
Menthol .....	0.9
Alcohol .....	18.0
Bentonite, 6%, in Lime Water .....	ad 120.0

**Pastes.**—When the acute inflammation has subsided, the use of an oily preparation or a paste is indicated. C. J. White taught that when the skin began to look like a peeling whitewashed fence, then it was time for oily or greasy vehicles. Their action is more prolonged and they adhere to and soften the scales and crusts. A paste is a rather stiff preparation consisting of powders and the vehicle which may be glycerin, hydrocarbons, paraffin, petrolatum, animal or vegetable fats, lard, cocoa butter, yellow wax, various expressed oils, or mixtures of these. Those containing glycerin are watery pastes. Two examples follow:

Starch .....	12.0
Distilled Water .....	24.0
Glycerin .....	q.s. ad 120.0
Zinc Oxide,	
Talc,	
Glycerin,	
Distilled Water .....	aa 30.0

Those having a base of petrolatum, such as the official paste of zinc oxide, are the most popular. However, as too much zinc oxide is apt to cause a folliculitis on a hairy surface, I prefer the following<sup>5</sup>:

## ADVANTAGES OF HOSPITAL CARE

The modern hospital has much to offer the patient suffering from severe acute disease of the respiratory tract. Diagnosis may be arrived at rapidly and accurately by roentgenographic and other means. The bacteriologic examination of the sputum is more conveniently and more precisely accomplished if the patient is in a hospital than if he is elsewhere. Expert nursing care will assure accurate medication and is an important aid in assuring proper intake of fluids and measurement of urinary output, which are such important factors in prevention of complications when chemotherapy is employed. Oxygen therapy may frequently be helpful in shortening the course of the disease, and may even be lifesaving in unusual and complicated cases. The early detection of complications of pneumonia is greatly facilitated and prompt treatment of such complications assured. Serious toxic effects of chemotherapeutic agents employed in pneumonia, such as renal concretions, hematologic idiosyncrasies, drug rashes, drug fever and so forth, will be much easier to detect and to treat under hospital conditions of medical practice than under other conditions. Inadequate dosage or excessive concentrations of the chemotherapeutic agent in the blood are less likely to occur when the patient is under hospital observation and supervision than when he is not.

At the present time there is an inadequate number of physicians for civilian practice in many communities and each physician must take advantage of those facilities which will permit him to treat the maximal number of patients with maximal efficiency and minimal expenditure of time. When acutely ill persons are confined to hospitals many details of care may be delegated properly to interns, nurses and even lay employees with gain in efficiency of treatment. The physician in charge may visit a large number of patients during the time which might have been consumed in making only a few house calls. In some communities the shortage of hospital beds may be a limiting factor in the realization of this aim, especially during times of epidemics of disease of the respiratory tract as influenza.

## CHOICE OF SULFONAMIDE DRUG

Of the several sulfonamide drugs which are available and are known to be effective against pneumococcus infections, my colleagues and I have a preference for *sulfadiazine* at the present time. Sulfadiazine is easy to administer, yields very satisfactory blood levels, rarely produces undesirable side reactions and, above all, appears to be as effective as any of the other sulfonamide preparations which are available at this time. Our preference for it is also dependent upon the fact that our

electric mixer. I usually prescribe the oil-in-water type of emulsion, because I want the medicament to reach the skin. This must be borne in mind when a water-soluble substance such as penicillin is incorporated in these vehicles.

In asymptomatic erythematous and papular eruptions, and macular, scaly eruptions such as pityriasis rosea, if there is no itching, there is no need of local applications. In pruritic eruptions, such as urticaria, there is no need for lotions containing insoluble substances. Simple watery or alcoholic solutions containing 0.5 to 1 per cent of menthol are more cooling and more antipruritic. *Astringent lotions*, such as the following,<sup>8</sup> are of value in acne.

Precipitated Sulfur .....	10.0
Spirit of Camphor .....	10.0
Alcohol .....	80.0
Solution of Methyl Cellulose, 2% .....	30.0
(1500 cps.)	
Rose Water .....	q.s. ad 240.0

**Ointments, Creams and Oils.**—It is in the use of the final category of dermatologic preparations that complications arise, namely in the use of ointments. I advise the inexperienced student to use an ointment as his last choice. Having no evaporating properties, being comparatively free of water, they cause congestion and irritation. However, when properly used, they are of extreme value. Their sale is, perhaps, the most profitable business of modern times. They are promoted as milady's creams for beauty, the rejuvenators of the old, the rectifiers of nutritional deficiencies, and the cure for all ailments from pneumonia to psoriasis. I saw one that was recommended for cardiac disturbances. They are the subject of tremendous research, and their value for introducing medication by absorption was recognized by the ancients, but apparently forgotten by many modern physicians. One must be mindful of the purpose for which he prescribes an ointment, must realize the danger of the absorption of the drug incorporated, and watch for untoward reactions locally or systemically. Many ointments are messy, obnoxious preparations, stain everything they contact, are difficult to remove, and cause a great economic loss, for, while the patient is using them, he dislikes to mingle with his fellow-workers and stops work.

A glance through pharmaceutical journals will show the efforts of the pharmacist to remedy these faults, which already have been recognized by the makers of proprietary preparations, with consequent increased popularity of their products. Again, the recent use of endocrines and sulfonamides, and the future use of penicillin have stimulated research for the vehicles by which they may best reach and penetrate the skin, an impossibility with petrolatum and lanolin. Fantus<sup>9</sup> listed the following ointment vehicles: cerates, ointments, cream ointments (cold creams). The cerates, due to the presence of

*Sulfapyridine* is rarely used by my colleagues and me at the present time in the treatment of pneumonia. British publications continue to refer to sulfapyridine in such a manner as to lead to the belief that the drug is still favored in England and in Canada. This preference may be due to the fact that sulfathiazole and sulfadiazine are not so readily available in these countries as sulfapyridine. However, definite information on this point is not available to us at the present time. Sulfapyridine has the very definite disadvantage of producing nausea and vomiting among a large proportion of patients who receive therapeutically effective doses. Furthermore, I do not know of any convincing evidence of any therapeutic property of this drug which is not possessed to an equal or greater degree by more recent sulfonamide derivatives.

*Sulfamethazine* has properties similar to those of sulfamerazine with even greater solubility in urine. Preliminary studies have also shown a high degree of therapeutic efficacy of this preparation but its complete clinical evaluation has not been accomplished at the present time and the drug is not available on the market.

*Sulfanilamide* has been supplanted completely in cases of pneumococcic infections and should not be employed in such cases, as it is distinctly inferior to the newer derivatives. *Diaminodiphenylsulfone* has been shown experimentally to possess a great therapeutic power but its toxic reactions are very severe and dangerous and the drug has not been released for sale because of this fact. Derivatives of diaminodiphenylsulfone have been prepared that have marked reduction of toxic potentialities but none of these are available in the market at the present time and these derivatives need not receive further discussion unless they become available to the medical profession.

The ideal chemotherapeutic agent for treatment of pneumonia remains to be developed, but progress toward that goal has been rapid and is continuing at an accelerated pace.

The inclusion of small amounts of some of the newer emulsifying agents in ointment bases facilitates their removal from the body. This is exemplified in the formula which follows,<sup>11</sup> in which the base consists of diglycol stearate, 5 per cent, and petrolatum, 95 per cent:

Crude Coal Tar .....	2.0
Zinc Oxide .....	2.0
Starch .....	15.0
Base .....	15.0

Many excellent washable bases have been recommended by Duemling.<sup>12</sup> In the use of tar, I have had excellent results with the following:

Crude Coal Tar .....	2.0
Sodium Lauryl Sulfate .....	0.8
Cetyl Alcohol .....	15.0
Glycerin .....	5.0
White Petrolatum .....	14.0
Distilled Water .....	35.0

The base whose formula follows is an excellent vehicle for ammoniated mercury, phenol, tannic acid, zinc oxide and ichthammol but is not suitable for boric acid and salicylic acid:

Glyceryl Monostearate .....	15.0
Cetyl Alcohol .....	15.0
Glycerin .....	35.0
Diethylene Glycol .....	35.0

A base which is compatible with all of the substances mentioned above has been recommended by Beeler:<sup>13</sup>

Cetyl Alcohol .....	15.0
White Wax .....	1.0
Propylene Glycol .....	10.0
Sodium Lauryl Sulfate .....	2.0
Distilled Water .....	72.0

Cetyl alcohol has the chemical formula  $\text{CH}_3-(\text{CH}_2)_{14}\text{CH}_2\text{OH}$ . It is manufactured by E. I. Dupont de Nemours, Inc. of Wilmington, Delaware, who also market sodium lauryl sulfate under the trade name of Duponol C. Cetyl alcohol is greaseless, a good emollient, and renders the skin velvety. Its penetrating power in combination with a wetting agent such as sodium lauryl sulfate causes medicaments to be readily transferred through the skin. The effectiveness of wetting agents is based on their power of reducing surface tension between solid and solvent, thus permitting rapid penetration and dispersion of the solid. Because of this property they are useful as detergents and penetrants, and some of these agents are also efficient emulsifiers. Propylene glycol ( $\text{CH}_3\text{CHOH}-\text{CH}_2\text{OH}$ ) imparts ease of spread and softness, and retards the evaporation of water. The above ointment base has been shown to be of the oil-in-water type. Its pH is reported to be within the range of 7 to 9, and is, therefore, well on the alkaline



ulcerative colitis" are descriptive of the serious nature of the disease and its pathologic inception and go far in depicting a disease entity. However, since in this discussion it is my aim to indicate the desirability of giving a particular sulfonamide drug or drugs for each form of colitis, I shall refer to this type as streptococcal ulcerative colitis.

This disease has characteristic pathologic manifestations and hence typical proctoscopic and roentgenologic features. Its lesions begin in the most distal segment of the rectum, just above the anal canal. Diffuseness of involvement of the bowel is its pathognomonic feature. Whether 1 inch (2.5 cm) of the lower part of the rectum or 5 feet (1.5 meters) of bowel are involved, the involved segment always is affected in its entirety, its entire circumference and the deeper layers of the wall and the mucosa secondarily. This feature gives the granular, easily bleeding mucous membrane so characteristic of streptococcal ulcerative colitis. The disease tends to spread upward until the entire colon, and even the lower part of the ileum in the late stages of the disease, become involved. Since streptococcal ulcerative colitis is primarily a disease of the intestinal wall, a very characteristic roentgenologic picture develops. The bowel becomes diffusely narrowed, haustral markings are erased, the flexures and curves become more angulated than normal and the result is a smooth tube. In this respect, streptococcal ulcerative colitis differs from all other forms of ulcerative intestinal disease, except perhaps regional enteritis when it is confined to the distal portion of the ileum. The latter condition has, however, many features to distinguish it from streptococcal colitis. Because of the relatively high incidence of the streptococcal form of ulcerative colitis and because of the consistency with which its clinical, proctoscopic and roentgenologic manifestations conform to a certain pattern, I am inclined to use this type of ulcerative colitis as a norm and to describe other types chiefly by noting in what respects they differ from it.

This form of ulcerative colitis manifests itself in a variety of ways but in general the clinical manifestations follow one of three general courses. When the lesions are limited to the lower segments of the large intestine, particularly the rectum and rectosigmoid, the onset of symptoms can be described as insidious. The patient may have normal motions of the bowel but in addition may pass two or three or many bloody, purulent rectal discharges. He may not have any other important systemic symptoms except that he will gradually begin to speak of not feeling well. His feeling of not being up to par may increase gradually as the number of rectal discharges increases and ultimately a mild form of diarrhea may develop.

spread on thinly. However, in acne rosacea, my favorite is the following:

Salicylic Acid .....	2.0
Precipitated Sulfur .....	2.0
Petrolatum .....	q.s. ad 30.0

This formula is also of great value in impetigo contagiosa.

Recently, extensive studies have been made in the use of the cutaneous route,<sup>21-24</sup> rather than injection, of drugs such as endocrines. In prescribing ointments, we must always remember the effect desired for the drug incorporated, and watch for undesired effects.

### INJECTIONS

In 1931 I reported the effect of calcium in pruritic skin affections, with special reference to calcium gluconate, a new compound in this country.<sup>25</sup> Before this paper was published, a patient with pernicious vomiting, who had miscarried twice as a result of the affliction, was given calcium gluconate intravenously for a severe attack of urticaria, with successful elimination of the urticaria and the vomiting. Thus a dermatologist may have been a pioneer in this field. However, when I see patients today who have had injections of calcium gluconate day after day, week after week, with no results except the depletion of their pocketbooks, I wish I had never published that report. It is of value in a few acute conditions, but after a few injections calcium can be given by mouth with the same satisfactory result.

The same holds true for other forms of calcium. Calcium chloride is very irritating and painful, if any of the solution extravasates into the tissue. Calcibronat intravenously and orally gives temporary relief to tense sufferers of neurodermatitis, but it should not be used too long because of the danger of bromism. Sodium iodide intravenously had a vogue in herpes zoster; I saw one good result in a case of herpes zoster ophthalmicus but in other cases this treatment appeared valueless.

Several cases of carbuncles and furunculosis appeared to be benefited by the use of aolan, but it became unpopular in my practice after abscesses appeared at the sites of injection in two patients. Collosal manganese seems to be of value in an occasional case of sycosis vulgaris, but useless in other diseases. Sodium thiosulfate gives transient relief from itching in cases of dermatitis exfoliativa from drugs, but I do not believe it shortens the duration of the disease. Although it has been claimed that the subcutaneous injection of sodium thiosulfate in situ is a means of preventing inflammation and pain after the accidental extravasation of the salvarsan, I prefer the injection of novocaine into these areas.

Enesol, a proprietary compound containing both arsenic and mercury, is of value in the acute cases of lichen planus. However, since it has not been available, I have used bismuth subsalicylate with almost

toms A drug that has wide limits of safety and relative lack of toxicity and is excreted rather rapidly was found to be *neoprontosil* (azosulfamide) Our experiences with this drug in the streptococcal form of ulcerative colitis have been very gratifying With a concentration of 2 to 4 mg per 100 cc of blood satisfactory response occurs in many cases To attain this concentration in the blood stream, a dose of 60 to 75 grains (4 to 5 gm) in each twenty-four hour period usually will be required for an average sized adult For children the dose will be correspondingly smaller Even with neoprontosil, however, toxic reactions may occur Hence, it has been my custom to start treatment by giving 5 to 10 grains (0.3 to 0.65 gm) every four hours by mouth and increasing this gradually until the desired dose is attained I then allow the patient to take the drug for two weeks, rest a week and then take it another two weeks If the concentration of the drug in the blood, concentration of hemoglobin, leukocyte count and sedimentation rate are followed carefully, an indefinite number of such courses may be administered However, if improvement follows the administration of neoprontosil, it will occur during the first or at least during the second course of the drug

My colleagues and I have given several other sulfonamide derivatives less toxic and of greater therapeutic effectiveness than sulfanilamide in treatment of streptococcal ulcerative colitis and others of even greater effectiveness undoubtedly will be made available Therefore, if response to neoprontosil is not satisfactory or if toxic reactions occur—and they may occur even from this drug—we have found sulfathiazole, sulfadiazine, sulfaguanidine, sulfasuxidine and sulfathalidine to be effective in selected cases of this form of colitis All of them are best administered according to the general method described, giving the drug for two weeks, allowing the patient a rest of a week and giving it again

Sulfathiazole is well tolerated in doses of 45 to 75 grains (3 to 5 gm) daily and sulfadiazine in similar doses, but much larger doses of sulfaguanidine are required for therapeutic effectiveness Sulfaguanidine again is a drug of relatively low toxicity and one of which large quantities can be brought into direct contact with the ulcerated intestinal surface When it is administered in doses of 150 to 180 grains (10 to 12 gm) a day, concentrations will average only 3 to 5 mg per 100 cc of blood

A combination of several of the sulfonamide drugs in a single case of colitis has often done more than one drug alone There may be a synergistic action among drugs of this series or at least among some members of the series Thus the administration of 40 to 50 grains

## THE SULFONAMIDES

The dermatologist, enthusiastic at first, early recognized the high incidence of sensitization from topical application of the sulfonamides, but despite his admonitions the general practitioner continued this use until he had a serious reaction in his own clientele. Although these calamities have become so numerous that now the lay public is cognizant and fearful, some pharmacists freely peddle sulfathiazole ointment over their counters and the two largest producers of band-aids continue to incorporate this dangerous drug in this universal first-aid application despite the fact that they are aware of the unfortunate results and of the resolution adopted by the Section of Dermatology and Syphilology of the American Medical Association.

The various sulfonamides are effective in the treatment of infections of the skin due to aerobic organisms such as streptococci and staphylococci. Sulfathiazole is more effective than sulfadiazine, sulfanilamide or sulfapyridine and is the drug of choice. The literature in 1941 advocated its use especially in impetigo. Later, sensitizations began to appear and it was recommended that it be used not over four days. The ointments containing as little as 5 per cent of sulfathiazole were found to cause the largest number of untoward results. Aqueous solutions, lotions and powders cause fewer accidents. However, approved textbooks do not recommend their use, because there are many harmless, time-honored remedies which are satisfactory for the relief of this minor disease.

I am thoroughly opposed to the topical application of these drugs, except in illnesses where withholding them might endanger life or lead to permanent disability, because I have seen too many cases of dermatitis exfoliativa of several months' duration in which the patient suffered untold torture unnecessarily. My worst cases have followed its use in varicose eczema.

All physicians are aware of the dangers of the oral use of the sulfonamide drugs, and as a result any untoward reaction is suspected by the patient owing to previous instruction by his physician, and subsequent confirmation leads to cessation of the drug. Most patients taking these drugs are hospitalized and under close observation, and the all too-frequent cutaneous reactions are readily recognized. With trepidation, I still use these drugs by the oral route in extensive pyogenic infections. I have used them in severe acne in large doses without success. Sulfapyridine, however, has a definite value in some cases of dermatitis herpetiformis. Physicians must remember the photosensitizing properties of the sulfonamides and not expose their patients to sunlight, ultraviolet or x-ray radiation while under treatment with them.

I have come to the conclusion that the dangers of the use of the sulfonamides in the practice of dermatology outweigh their benefits.

three or four weeks, a striking transformation of the proctoscopic appearance of the lesions has been noted. Frequently, however, the disease process has returned within a few weeks after the administration of the drug had been stopped. The daily use of retention enemas of sulfanilamide (60 grains [4 gm.] of sulfanilamide) has resulted in complete healing of the proctitis in several months. A combination of administration of the drug by mouth and by rectum has yielded better results than either method alone. With every method careful studies of the blood for effect on hemoglobin and leukocytes as well as of concentration of the drug in the blood are important.

The recession of the rectal stricture, sometimes to almost complete disappearance, as a result of the administration of sulfonamide drugs has been striking in some instances. The administration of *sulfaguanidine* in doses of 10 gm. daily over a period of several months has been associated with progressive improvement of the local lesion, as well as general improvement such as gain of weight and general euphoria. The number of rectal discharges has decreased from between fifteen and twenty a day to between two and six and bleeding has stopped. The rectal stricture has been known to become softer and the adjacent rectal wall thinner and pliable.

*Sulfathiazole* has also been used with success. The inguinal variety of venereal lymphogranuloma in particular has responded well to administration of 1.5 gm. of sulfathiazole three to five times a day for three weeks, followed by 1 gm. three to five times a day for another three weeks. In many cases proctitis and early formation of stricture have also yielded readily to such treatment. The advent of more marked stricture will, of course, extend the duration of the treatment. Then one should give the drug in courses, giving it for two or three weeks, allowing the patient a rest of a week and giving it again.

#### REGIONAL ULCERATIVE COLITIS

Another type of ulcerative colitis in which the lesions usually are limited to the large intestine is one of which the cause is not clear. We speak of it as a regional type of ulcerative colitis. The lesions involve isolated segments of intestine. They may involve any segment, much in the manner of regional ileitis except that here the site of the disease is the colon. The lesion may be subacute or chronic and usually is quite destructive but also there may be evidence of hyperplastic changes. Commonly segments of the intestine from 6 to 12 inches (15 to 30 cm.) long are found to be involved, whereas the portions of the bowel distal and proximal to the lesion are entirely normal and the rectum is never involved. In other words, this segmental type of colitis

use in congenital syphilis, and late cutaneous and osseous syphilis, with excellent clinical results. Although in my opinion late cutaneous lesions do not respond as rapidly as they did to the old arsphenamine and potassium iodide, still response is fairly prompt. It must be remembered that the use of penicillin is still in the stage of investigation, and positive assertions regarding cures cannot be made until at least a five- or ten-year period has elapsed. Perhaps later the administration of penicillin with an arsphenamine or heavy metal may be the method of choice. However, any drug properly administered at the right time that will give 80 per cent apparent cures must be considered remarkable.

As penicillin became more available, it was used in various cutaneous disturbances, especially those of staphylococcal or streptococcal infection, with varying success. Three cases of severe disseminated lupus erythematosus, two of pemphigus and one of erythema induratum failed to respond to penicillin. One case of hydradenitis responded promptly to 600,000 units, but recurred in a short time. Several cases of extensive cystic acne vulgaris involving the face and entire back had marked temporary improvement, but with the cessation of the injections new lesions immediately appeared, necessitating the regimens previously used in the treatment of the disease. The same was true of sycosis vulgaris. In these cases as high as 2,000,000 units were used with improvement; the eruption recurred after cessation of treatment.

Various types of local applications were used and finally a water-in-oil emulsion was prepared that was found satisfactory. While this preparation has not cured the disease it has markedly reduced the number of lesions, to the satisfaction of the patient. It has been found of value in impetigo contagiosa, provided that the usual cleansing methods are employed, namely washing the face with soap and water and removing the crusts.

One case of pemphigus neonatorum was successfully cured. Two days after birth the patient showed a bullous eruption which rapidly involved nearly all the cutaneous surface. Various sulfa drugs were used internally and externally with no improvement—the eruption continued to spread. On the eighth day I saw the patient and prescribed penicillin. Nineteen injections were given in two and a half days—eight doses of 5000 units and eleven doses of 2500 units—as well as local application of compresses of saline containing 500 units of penicillin per cubic centimeter. The response was almost immediate—within twenty-four hours the patient's temperature dropped, no new lesions appeared, and the old ones rapidly desquamated. In three days the skin was entirely healed except for two extremely adherent crusts, one on the left cheek and one on the right side of the neck. It was interesting to note that a small extremely adherent crust on the side of the neck was frequently daubed with a compress containing saline and penicillin. On the sixth day a reaction of irritation or hypersen-

millimeter of blood The sedimentation rate (Westergren's method) was 105 mm the first hour The lining of the rectum for 30 cm appeared to be normal No unusual parasites, ova or bacteria were found in the stools Agglutination tests



Fig 63—The deformity of regional ulcerative colitis involving the colon from the midascending to the midtransverse segment

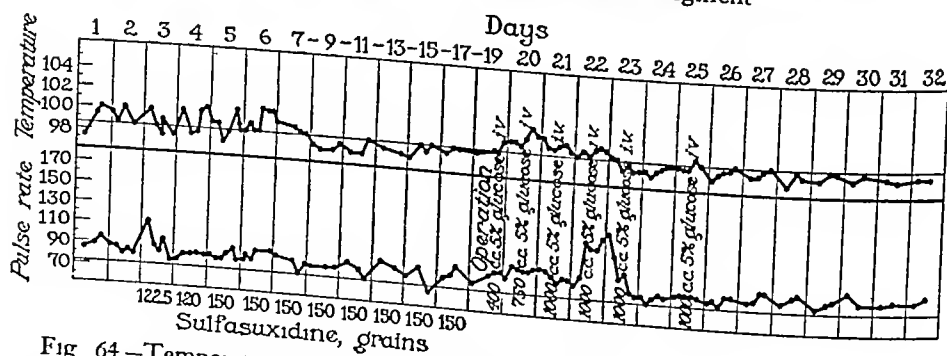


Fig 64—Temperature and pulse rate of the patient referred to in Figure 63, who had regional ulcerative colitis, while she was taking sulfasuxidine and being prepared for surgical treatment.

for organisms of the *Shigella paradysenteriae* group gave negative results The roentgenologic examination revealed ulcerative colitis involving the colon from the midascending to the midtransverse segment (Fig 63)

also cited carotinemia, which may result either from ingestion of only moderate excess of carotene, or from impaired ability of the body to metabolize the amount of carotene present in a normal diet. I have seen cases of generalized pruritus which were relieved when the patient stopped taking large doses of vitamin B.

*Vitamin A* should be tried in follicular hyperkeratosis, keratosis pilaris, pityriasis rubra pilaris, keratosis follicularis, and loss of skin tissue as from burns and ulcers. It should be given in daily doses of 200,000 units.

*Vitamin B complex* has been used in many cutaneous diseases with varying success. Favorable results in acrodynia by the injection of 6 mg. daily for six days were attributed to thiamine. Occasionally it seems to lessen the pain of postzoster neuritis,<sup>31</sup> though this relief may be somewhat psychic. Riboflavin has established its place in the treatment of the syndrome of cheilitis, perlèche, the brilliant-red, smooth tongue, and the scaling and keratotic plugging of the seborrhoeic area of the face, when given in doses of 20 mg. daily. If given with accompanying doses of dilute hydrochloric acid, it is useful in the cutaneous eruptions and keratitis of acne rosacea. Recently I have been giving large doses in the treatment of the discoid type of lupus erythematosus with some success. Nicotinic acid has been a lifesaver in pellagra. It seems to be of value in the acute pyogenic infection. Pyridoxine has been recently reported as being of value in acne.<sup>32</sup> Liver extract parenterally or orally combined with iron certainly helps the adolescent chlorotic miss with acne.

Crandon and his associates<sup>33</sup> proved the need of *vitamin C* in certain types of hyperkeratotic lesions, petechial hemorrhages, and failure of wound healing. Sulzberger found that large amounts of vitamin C will raise the sensitivity threshold and that there will consequently be less danger of reaction to the use of the arsphenamines in syphilis. Cornbleet<sup>34</sup> showed its value in the removal of melanin deposition of Addison's disease.

Despite the many reports of the value of *vitamin D* in psoriasis, acne vulgaris, pemphigus and scleroderma, in my hands it has been a failure. It stimulates healing in x-ray burns.

*Vitamin P* is recommended in purpuras and for regulating vascular permeability, but not sufficient work has been done to prove this contention.

Vitamins to be of value must be used in adequate dosage and though they apparently are harmless, we still have a great deal to learn about them. They are expensive. The lay public is thoroughly victimized and vitaminized by advertising propaganda, and it is the physician's place to stem this tide, unless a definite deficiency in the patient is recognized.



nounced features of advanced disease are frequently apparent and the diagnosis can be established readily

As with many chronic infections of a proliferative and destructive nature, the history of regional ileitis frequently begins with the complaint of fatigue, general malaise and loss of weight. At the time of onset of these symptoms or soon after, a patient will complain of a mild, usually intermittent, type of diarrhea. The stools will be loose and watery, and defecation will be associated with cramps. Periods in which normal or even hard, dry stools are passed may alternate with periods of diarrhea. The history in these respects is similar to that of a patient who has intestinal tuberculosis. As a rule, however, in cases of regional ileitis, progression to the next phase is more rapid and symptoms are more severe than in cases of intestinal tuberculosis. In the former, attacks of abdominal pain soon supervene and the pain may be of the dyspeptic or obstructive type from the first. In either event, obstructive features will soon predominate.

Generally speaking, there are four phases of the disease. The earliest manifestation is that of an acute inflammatory process. As the terminal portion of the ileum is the most frequent initial site of the disease, irritation of this portion of the intestine and its adjacent peritoneal covering produces a picture difficult to distinguish from acute appendicitis. The most common symptoms are fever of low grade, leukocytosis, nausea, vomiting, and tenderness and pain in the epigastrium or right lower abdominal quadrant. Diarrhea and cramps are unusual at this stage of the process.

As the disease advances, intermittent attacks of diarrhea are characteristic. The typical syndrome of enteritis of low grade then prevails, for the patient has fever, anemia and a palpable mass in the right lower abdominal quadrant and has lost weight, his stools are loose or watery and if any pain is present it is mild and colicky.

Remission of symptoms is common in the two stages described but, as the stenosing effects of the disease increase, the periods of relief are shorter and occur less frequently than before. The symptoms typical of intestinal obstruction are superimposed on those of chronic enteritis. The attacks of diarrhea are more profound than before and are accompanied by severe abdominal cramps, borborygmus, abdominal distention or visible contracture of the coils of the small intestine proximal to the diseased segment. Malnutrition and anemia become prominent features, since the intestinal wall does not absorb much of the nourishment and fluids because of the diarrhea. Furthermore, intake may be greatly limited on account of persistent nausea or even vomiting.

The combination of crude coal tar and ultraviolet ray in the treatment of psoriasis has been used in Boston for many years with great temporary success. The tar is rubbed into the skin before ultraviolet radiation. Goeckerman,<sup>35</sup> however, perfected this treatment and first reported its success with patients at the Mayo Clinic.

### CONCLUSION

This article may seem to be one of destructive rather than constructive criticism. However, it is the result of many observations made in private practice. It is an attempt to add emphasis to the fact that many cutaneous diseases are self-limited, and are best treated conservatively with well-established beneficial methods of therapy. It is not an attempt to condemn experimental research for new advances, but to advise the physician to wait for results obtained by scientific experimentation developed by recognized clinics especially equipped for this type of work.

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gradually into a chronic state. In either event, a rather typical form of ulcerative colitis supervenes. While in these cases cultures of stools will almost invariably be negative, the high serologic agglutinin titer in the blood against one or the other of the strains of *Shigella paradysenteriae* may help in establishing a diagnosis. The following report of a case is illustrative.

CASE II—An unmarried woman, aged nineteen years, from Chicago, was brought to the Clinic on October 13, 1943, in an ambulance, because of severe bloody diarrhea which had been present since a spell of diarrhea starting while she was on a vacation at camp in August, 1943. Although she had had continual trouble since then, there were periods when she had been better and periods when she had been worse, the last month being particularly bad.

On admission, the appearance of the patient was that of an obviously sick girl. During the first ten days the temperature ranged between normal and 105.5°

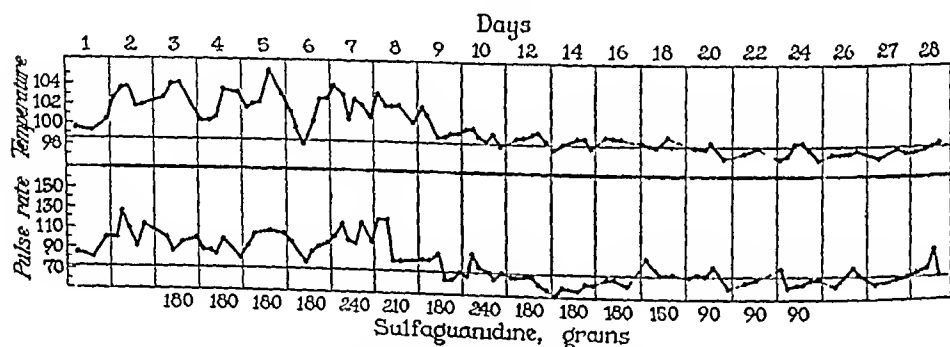


Fig. 65—The course of the temperature and pulse rate of a patient who had severe ulcerative colitis following bacillary dysentery. The colitis was treated with sulfaguanidine.

F (Fig. 65). Her stools were large and consisted mostly of bloody pus to the extent of half a bedpanful at a single discharge. The proctoscopic examination revealed numerous superficial mucosal ulcers. When the condition of the patient warranted it, which was not until three weeks after admission, a roentgenologic examination of her colon revealed extensive ulcerative disease involving mostly the transverse colon. The concentration of hemoglobin was 9.4 gm in each 100 cc millimeter of blood. The sedimentation rate (Westergren's method) was 110 mm the first hour. Numerous stools were examined. No unusual parasites, ova or bacteria were found. A serologic agglutination test gave a reaction positive for *Shigella paradysenteriae* (Flexner) in dilutions of 1:1,280.

Beginning with the third day, the patient was given 240 grains (16 gm) of sulfaguanidine in divided doses each twenty-four hours (Fig. 65). By the end of a week her temperature did not go above 99.5° F. Administration of sulfaguanidine was then continued at 90 grains (6 gm) daily in divided doses. During the patient's last week in the hospital, her temperature was normal and she passed only one stool a day and felt entirely well. Serologic agglutination tests during

## THE TREATMENT OF EPILEPSY

WILLIAM G. LENNOX, M.D.\*

IN the treatment of every disease, increased knowledge about that disease brings new opportunities and added responsibilities for the physician. Chemotherapy, for example, means added years of life for the patient, but also increased reading and study for the doctor. Tragic is the fate of the patient whose doctor has not been able to "keep up" with newly gained knowledge.

In recent years the gains against epilepsy have been as real, in relation to former knowledge, as those against infectious diseases, yet most patients, after visits to many doctors, are bewildered, discouraged, and still convulsing. This need not be. Epilepsy can no longer be classed as a "cause unknown" disease. The physician has at hand therapeutic weapons, both medicinal and social, which were lacking a dozen years ago. By means of the electroencephalograph, he can now look behind the patient's variegated and unpredictable seizures to the disordered electrical pulsations of his brain and thus gain a better insight into the type and extent of the disorder, and more intelligently select the drug most likely to succeed. The half million epileptics in the United States cannot be treated by a few specialists. The average epileptic must look to his own doctor, hoping that this doctor has sufficient interest in him and his problems and sufficient medical knowledge to give him treatment which is not traditional but modern.

Treatment of seizures cannot be instituted until two questions have been considered. First, is this person really epileptic? Second, what conditions in this particular patient are responsible for his seizures?

### IS THIS EPILEPSY?

The diagnosis of epilepsy seems disarmingly easy because the word describes a symptom or group of symptoms. Epilepsy is the Greek word for "seizure" so that any one who comes to his physician with the story of repeated sudden loss of consciousness, possibly with accompanying involuntary muscle movements or peculiar actions, is by definition an epileptic. However, by common consent various seizure phenomena have been set aside as nonepileptic. These include syncope, episodes which resemble syncope but are due to an irritable carotid sinus, periods of unconsciousness or amnesia due to hysteria, convulsions which occur in the course of toxemia of pregnancy, or uremia, or which are directly due to hypoglycemia, or to the ingestion

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From the Department of Diseases of the Nervous System, Harvard Medical School, and the Children's Hospital of Boston.

\* Assistant Professor of Neurology, Harvard Medical School; Visiting Neurologist, Boston City Hospital; Visiting Physician, Children's Hospital of Boston.

for three to five days to the average patient on whom colon resection is to be performed for a malignant lesion. The patient is given 16 grams (16 gm) in divided doses on the first day and 180 grams (180 gm) in divided doses each subsequent day until operation. Within five days is the average time required for preparation of the patient who has an uncomplicated, nonobstructive lesion, the time required if the lesion is perforating or penetrating may be much longer. In these cases particularly that sulfasuxidine and other drugs of the sulfonamide group have been particularly helpful.

The use of the sulfonamide compounds in the last several years has been a part of the preoperative program in the treatment of intestinal disease and has emphasized their value. It has become obvious that by the use of intestinal surgical treatment has definitely been made safer.

#### GENERAL CONSIDERATIONS

There are a number of intestinal conditions in which various members of the sulfonamide group have been tried. In a few conditions the use of sulfonamide compounds has met with relative success but in conditions other than those discussed their use has been associated with disappointment. Studies on animals and some clinical observations have suggested that the sulfonamide compounds might have value in the treatment of intestinal tuberculosis.

Some hope has arisen through studies on animals that the Asiatic cholera might be conquered by the use of sulfonamides. Clinical experience so far is small and the results are rather disappointing, although physicians that have used these drugs in treating patients suffering from this condition have felt that they probably should have used the drugs in too small amounts.

There is no evidence so far that typhoid fever will be affected by any of the sulfonamide drugs. Some forms of gastro-enteritis in children have apparently responded in a rather striking way to the administration of some of the sulfonamide compounds. There are still conditions in which some improvement has been noted with the use of that drug but the reports are so sporadic that no conclusions can be drawn as yet. There will undoubtedly be other intestinal conditions in which will be benefited with the passing of time and increased experience with the use of these drugs.

3. *Grand Mal*. A convulsion, tonic and then clonic, involving the whole body, with unconsciousness. Electroencephalogram: Generalized high voltage fast waves.

4. *Psychomotor, or Psychic Equivalent Seizure*. A period of amnesia with or without tonic spasm or contortion of trunk muscles. The person may appear to

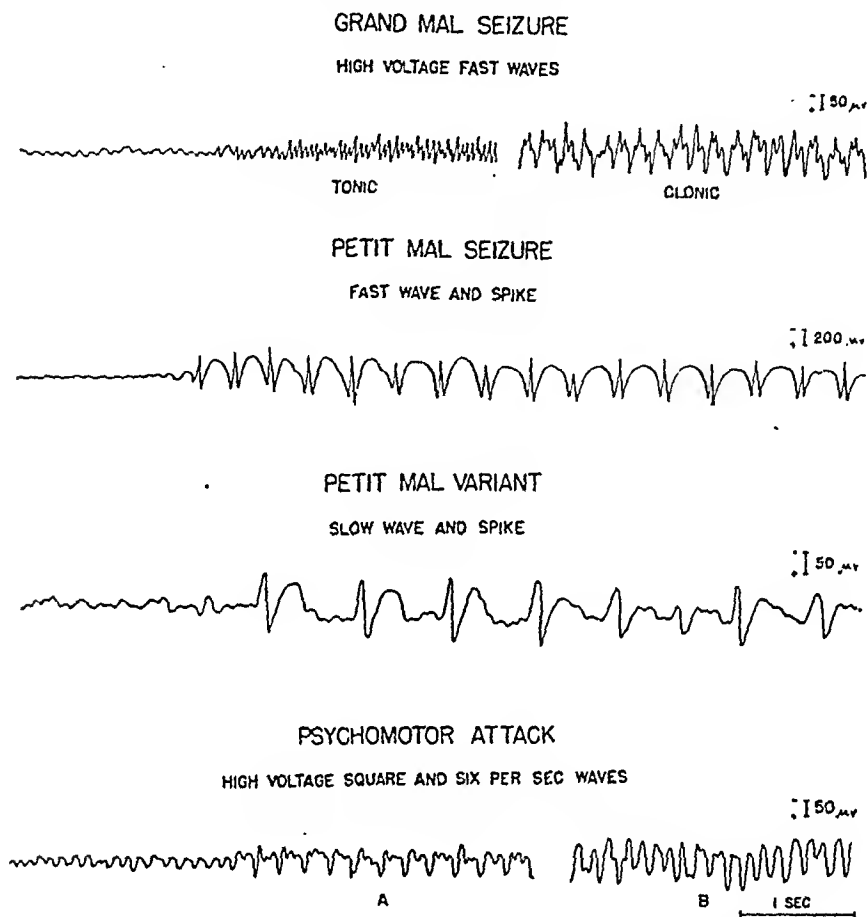


Fig. 162.—The four different patterns of waves observed during four different types of seizures, grand mal (including jacksonian and focal), petit mal (also called pykno-epilepsy), petit mal variant (in which the association of seizure discharges and clinical symptoms may be vague or absent) and psychomotor. In each case the left hand portion of the tracing is the person's normal record. A and B in the bottom tracing represent different stages in this particular patient's seizure. The horizontal line at the bottom indicates one second, and the perpendicular lines at the right the signal made by 50 or 200 microvolts of current. (Gibbs, F. A., Gibbs, E. L. and Lennox, W. G.: Arch. Neurol. & Psychiat. 41: 1111 [June] 1939.)

act in a normal manner, or be confused or mutter, make chewing motions, have a "running fit," or become immobile with slow rotation of the body. Manifestations are of extreme variety, often leading to the mistaken diagnosis of hysteria. The patient has no memory of events during the attack and may be unaware that the attack has occurred.

after Gram staining in a large percentage of cases. It is a gram-positive coccus and grows in chains. It is not spherical but ovoid and the long axis of each individual organism is on the long axis of the chain. I do not pretend that this is a positive identification but it is a clinical aid.

The last point I wish to mention is the positive need for complete urologic examination in all cases in which infection of the urinary tract does not respond to one or two courses of sulfonamide therapy. The startling difference in the results obtained from treatment in cases of uncomplicated infection from those obtained in cases of infection in which stone, tumor, obstruction or chronic inflammatory changes are associated is so great that the possibility of complications must always be kept in mind.

In closing I wish to make a plea for a more careful and scientific approach to the treatment of infections of the urinary tract. After all, the story is a simple one and can be told simply in the majority of cases. An exact appreciation of the causative organism and the underlying pathologic features should be obtained in all cases. Dosages should be kept low and the ever impending possibility of crystallization in the urine, particularly of the newer compounds, sulfadiazine and sulfamerazine, should always be borne in mind.

suggesting congenital maldevelopment of the brain, a story of birth injury, of cerebral or meningeal infections, or of certain cerebral diseases of later life, such as trauma, syphilis, tumors, or cerebral circulatory disorders. Second, a description of jacksonian seizures or of aura or convulsive movements confined to one side of the body. Third, neurological signs indicative of cerebral pathology. Fourth, laboratory evidence of cerebral pathology derived from roentgen rays of the skull or of the ventricular system (pneumoencephalogram) or from the electroencephalogram. In appraising the etiologic importance of brain pathology, the damage must have antedated the epilepsy, and not be merely the result of subsequent falls or convulsions.

**The Electroencephalogram.**—Much the most important tool for determining the diagnosis, and the causes of seizures, and in guiding treatment is the electroencephalograph. Unfortunately this technic will only slowly become generally available. The apparatus is expensive and some widely advertised types are wholly unreliable. The making of satisfactory records and their proper interpretation requires even more experience and skill than the electrocardiograph. Artifacts may be confusing; the frequency and voltage of waves are modified by activity of brain or body or by sharp alterations in body chemistry, hence records must be made under standard conditions. However, the cost and trouble involved in obtaining dependable brain wave tracings is as nothing compared with the cost of epilepsy and the difficulties of treating it without the aid of this technic.

As with most other laboratory devices the electroencephalogram supplements but does not supplant diagnoses made from the description of seizures. The significance of a record varies with the degree of its abnormality. In a group of 1260 patients diagnosed as epileptic on clinical grounds, in 13 per cent the electroencephalogram was considered normal; in 29 per cent the waves were only moderately slow or fast, and hence weakly support a diagnosis made on clinical grounds; in 20 per cent waves were very slow or fast, and hence suggestive of epilepsy. In 38 per cent there were paroxysmal discharges of high voltage fast or slow waves, which are strongly suggestive of epilepsy. Half of these records with seizure discharges (19 per cent of all patients) were of the alternating dart and dome formation, which is diagnostic of petit mal.

The relative significance of various patterns is shown by their distribution in 730 adult epileptics, and in 1260 "normal" persons. Thirty-three of the epileptics had tracings with bursts of high voltage waves (seizure discharges) for each nonepileptic with this sort of tracing. The corresponding ratio for tracings with very slow or very fast waves of usual voltage was 20 to one; and for tracings with mildly slow or fast waves the ratio was two to one. For normal tracings the ratio was one in the epileptic group to six in the normal group.<sup>1</sup> In addition to giving substantial confirmation of the diagnosis in one-half



tialities for toxicity if the infection is one for which it is known as a fact that chemotherapy is of no value. The two organisms most commonly encountered as etiologic agents in puerperal and postabortal sepsis are the Group A (Lancefield) hemolytic streptococcus and the anaerobic streptococcus, especially the organism described in 1910 by Schottmuller. In cases wherein the former organism is identified, sulfonamide compounds have definite value, but in cases in which the latter organism is identified they are without known effect. There is a sharp difference of opinion as to the relative incidence of these two organisms in the causation of puerperal sepsis and perhaps there are differences of locality, type of clientele and other factors that modify the relative incidence of these two types of infections in pregnancy. The sulfonamide compounds are of value in the less common infections of the parturient genital tract by *Clostridium perfringens* but they must be given early and in large doses to be of the desired aid.

Another rare type of puerperal infection is that caused by staphylococci (*aureus* or *albus*). Early treatment with penicillin here promises much. There is some evidence that leads one to hope that penicillin will be helpful in combating the anaerobic streptococcus of Schottmuller. This type of sepsis, when well established in puerperal patients, has been almost invariably fatal.

Discussing the hemolytic streptococcal type of puerperal sepsis, Colebrook and Purdie<sup>8</sup> showed that the fatality rate in cases of bacteriemia in which treatment was given as compared with the fatality rate in cases in which treatment was not given has been decreased from an average of 71 to 27 per cent. Chandler and Janeway<sup>9</sup> commented on the effectiveness of chemotherapy in this type of sepsis and explained the role of immunotransfusion when chemotherapy is used. When chemotherapy alone seems insufficient to cause improvement, the addition of immunotransfusion has seemed to effect this desired clinical improvement with eventual cure. Furthermore, the addition of blood from an immunized donor seemed to increase the effectiveness of small doses of sulfanilamide. Studdiford<sup>28</sup> reported results of chemotherapy in a small series of cases. His cases were well studied and there was presented a control series of equal size and character consisting of material observed in the years just prior to his first use of sulfanilamide in treatment of hemolytic streptococcal sepsis. For cases of septicemia or peritonitis or both the mortality rate was reduced from 83.5 per cent to 25 per cent. Studdiford noted that the two deaths in the treated series occurred early in the series, when smaller doses were in use than in later years. Diddle and Mengert<sup>10</sup> used sulfonamide compounds in seventy-six cases of puerperal sepsis. These cases varied in severity

of adhesions between the brain and meninges, or tying redundant blood vessels is of little or no avail. With careful selection of cases and expert surgical technic (plus postoperative use of drug therapy) the removal of cortical scars or superficial tumors may result in virtual freedom from seizures for as many as two-thirds of the patients. Any one contemplating neurosurgical attack on epilepsy should study the book by Penfield and Erickson.<sup>4</sup>

**Drug Therapy.**—The chief hope of controlling seizures lies in improving the chemistry of abnormally discharging nerve cells, through the administration of medicine. The physician now has a number of drugs from which to choose. Good results from treatment depend on discrimination in the choice of these and skill in determining the dosage best suited to the individual patient. No medicine should be continued unless adequate trial demonstrates that seizures are fewer or less severe with than without it. "Adequate trial" means daily use over months of time of each of the most effective drugs, each given in increasing amounts until either toxic symptoms appear—or seizures disappear. After two or three years of freedom (and an improved electroencephalogram) medicine may be stopped.

First we shall describe the various drugs and later discuss their choice.

*Bromides*, a phenomenal discovery when first used in 1857, are gradually assuming a place of historical importance only. For most patients they are the least effective of the anticonvulsants and, when given in considerable amounts, may cause unpleasant acneform eruptions and impair mental alertness. In order to maintain a certain level of bromide in the body, the chloride intake needs to be kept constant. A usual dose is 10 to 20 grains (0.6 to 1.2 gm.) of sodium or potassium bromide given three times a day in a watery solution.

*Phenobarbital* has been in use since 1912. It is also sold under the trade name of luminal at a considerable increase in price. Phenobarbital has the advantage of being easy to administer. After the optimum dose has been ascertained, patients may continue treatment for months or years with little supervision. The side-effects of this drug are a scarlatina-like generalized rash, in the rare person who is allergic to it, or loss of mental alertness if the dose proves excessive. Individual reactions vary widely. Some patients experience uncomfortable drowsiness with as little as one-half grain a day, whereas other patients can take as much as six or eight grains without noticeable effect. The drug may be used daily for many years without ill effect and without the establishment of habit. The amount may need to be increased from time to time. When taken in huge amounts by mistake or in suicidal attempts, the person experiences extreme ataxia and deep sleep amounting to coma. Phenobarbital is dispensed in tablets containing  $\frac{1}{4}$ ,  $\frac{1}{2}$  or  $1\frac{1}{2}$  grains (0.015, 0.03 or 0.1 gm.). For daily oral use the average adult dose is  $1\frac{1}{2}$  grain (0.1 gm.) which may be divided between

cause any case may be a potentially fulminating one. The dose should be spaced "around the clock" to maintain even absorption. The fluid output of patients receiving sulfadiazine or sulfathiazole should be 1,500 cc. or more. The maintenance of the urinary output and alkalization of the urine are the cardinal principles involved in the prevention of urinary complications.

Once a course of chemotherapy is embarked upon, it should be continued with determination unless there develops evidence of serious toxicity that cannot be treated successfully. Common examples of such toxicity are hepatic damage (jaundice) and severe leukopenia. Of course chemotherapy should be started early, before septic embolic phenomena or vegetative endocarditis develops.

In summary, the general opinion expressed in the literature is that chemotherapy with the sulfonamide compounds is of definite benefit in lowering the mortality rate of puerperal sepsis due to Group A (Lancefield) hemolytic streptococci. Its value for anaerobic streptococcal infections seems to be nil. It should be used early together with serum when sepsis is proved to be due to *Clostridium perfringens*. A few writers are somewhat skeptical of the value of chemotherapy, some apparently because in most cases of sepsis that they have encountered the infection has been due to anaerobes, and they justly deplore the extensive use of chemotherapy in cases such as these, in which its only effect would be deleterious owing to possible toxicity. My colleagues and I have felt, however, along with others that early in any fulminating sepsis an appropriate chemotherapeutic agent should be given in full doses while bacteriologic studies are in progress. In some cases a result of single intra-uterine culture may be fallacious.

It is true that many patients suffering from Group A hemolytic streptococcal sepsis who were adequately treated died. It is also true, on viewing the situation impartially, that many more who were treated received inadequate therapy because administration of the drug was stopped when toxic effects developed. In other cases chemotherapy was started too late. So far in the literature instances of toxic effects resulting from the administration of sulfathiazole and sulfadiazine are rare, possibly owing to their lower toxicity and perhaps in part because full reports of the results of those last two drugs are not at hand.

There seems to be no uniform opinion as to the value of routine prophylactic sulfonamide treatment for puerperal sepsis. Another form of chemotherapy perhaps deserves mention and reconsideration by those interested in obstetrics, namely, the *prophylactic instillation of antiseptic solutions*. Brown<sup>5</sup> stated that there were thirteen deaths from sepsis during the period 1924 to 1932 among 9,529 deliveries of pa-

sonable hope that early intensive treatment together with rest will effect a good cure as to normal physiologic function of the tubes and ovaries in many cases

Points in the history such as pain in the lower part of the abdomen, chills and fever together with pelvic findings and an elevated sedimentation rate indicate acute or subacute salpingitis. Possibly mild salpingitis may exist without the foregoing findings. Because of this (especially if fever exists), we have given somewhat higher initial doses of sulfonamide compounds than some physicians. We have used 5 or 6 gm in divided doses throughout the first two or three days. As the blood level and the patient's progress permit, the dose is decreased, usually to 1 gm every six hours for several days. The patient is usually now afebrile and cultures have become negative. If adnexal masses exist, pelvic heating by diathermy to 106 or 108° F for one or two hours a day is employed as valuable adjunct therapy. Progress in these latter cases is determined, of course, by diminishing pelvic findings and a falling sedimentation rate as well as by lessening of subjective symptoms.

Barrows and Labate<sup>2</sup> reported that, in 70 per cent of cases, mild salpingitis responded to chemotherapy if the latter was used within five days of onset. Masses palpable in the pelvis could no longer be detected after a week from the start of treatment. Only in 20 per cent of control cases in which chemotherapy was not used was such a result obtained. Even when salpingitis was moderately severe (when adnexal masses of 5 cm or more were palpable) favorable results were obtained from chemotherapy in 60 per cent of cases in which it was begun within five days of onset. The results of Barrows and Labate among patients who had had adnexal inflammation for more than five days were poor. Our own experience is in accordance with the foregoing report. However, we do favor an adequate trial of chemotherapy in cases of adnexal gonorrhea of longer duration than five days and even of great extent, since such treatment combined with pelvic heating will often yield worth-while salvage and at least shorten the period of illness unless the condition is hopelessly chronic. It also makes later necessary surgical treatment easier and safer.

It is common knowledge that cultures are more dependable as a test in the diagnosis and as a criterion of cure than smears. Our criterion of cure is at least three or four negative cultures, at least two of which should be postmenstrual. Adair and Hac,<sup>1</sup> using sulfonamide compounds in treatment of women suffering from gonorrhea, reported incidence of drug-fast patients as being only one in 453 patients. The incidence at the Clinic is higher than this.

Two innovations in chemotherapy may merit mention Pappas<sup>23</sup> employed single doses of 5 to 7 gm in treatment of male patients suffering from acute Neisserian infections and obtained cures of twenty-three of twenty-eight such patients treated. Results of doses of 5 gm were as good as those of doses of 7 gm Pappas quoted Miescher<sup>21</sup> as using single doses of 2 to 5 gm with good results, obtaining a transitory concentration of the drug (sulfathiazole) of 10 to 11 mg per 100 cc. of blood Bickers<sup>4</sup> employed local sulfonamide suppository treatment with good results

Such therapy as the Miescher-Pappas and the Bickers methods might be applicable, provided it was ascertained as certainly as possible that the infection was acute and was localized below the internal os In general, however, the method of treatment that we have outlined would seem more thorough and better controlled than the new methods described in the preceding paragraph

#### INTRAPERITONEAL CHEMOTHERAPY

The intraperitoneal use of sulfonamide compounds is as valuable in gynecologic surgical treatment in the presence of peritonitis or in cases in which soiling of the peritoneum cannot be avoided as in other such surgical conditions Waugh, McCall and Herrell<sup>25</sup> have recently reviewed the literature on the subject of intraperitoneal chemotherapy and have stated their experience in a large number of cases They expressed the belief that the sulfonamide drugs are relatively harmless locally and intraperitoneally if proper choice and use of them are made They further observed that little has been found to contraindicate the prophylactic use of these drugs in "clean" cases although the results so produced are naturally not as amazingly beneficial as for such conditions as necessitate operations on the colon or for perforating appendicitis In the latter conditions, intraperitoneal chemotherapy has been perhaps the chief factor in the reduction during the past three years of the mortality rate to a third or a fifth of what it was formerly It is well known that enormous concentrations of the drug (200 to more than 1 000 mg per 100 cc in the case of sulfanilamide) are obtained at the site of implantation and maintained for some hours, thenceforward to be lowered gradually *Sulfathiazole* and *sulfamylamide* are the drugs of choice Toxic reactions when present have usually been encountered among those cases in which systemic chemotherapy was started almost immediately after operation When possible, two or three days should be allowed to elapse after operation before such treatment is started The urinary output should be maintained at 1 200 cc per twenty four hours for the first ten to fourteen postoperative days

At cesarean section and especially when the membranes have long been ruptured and labor has proceeded for some hours, intra-abdominal chemotherapy should be employed. Certainly this should be done if actual or potential infection exists. Some of us at the Clinic use this treatment also in elective cesarean sections. It has been our impression that the drug deposited in the uterus is absorbed very abruptly through the large uterine sinuses and therefore we have deposited most of the drug under the peritoneal flap of the bladder in cases of low cervical cesarean section (along the uterine incision) and in the pelvis near the parametrium. McKelvey<sup>18</sup> has warned of the sudden absorption of sulfanilamide by the portal system as a cause of hepatic damage.

#### MISCELLANEOUS GYNECOLOGIC CONDITIONS

**Vaginitis**—Fletcher<sup>12</sup> and others have reported the local use of sulfonamide compounds in various types of vaginitis. Experience to date, while not conclusive, does not show it to be the specific which would be welcome for *Trichomonas* infection.

For Neisserian vulvovaginitis of infants chemotherapy has proved effective. Lewis<sup>17</sup> again reviewed this subject in 1941. He quoted Benson as curing 90 per cent of thirty patients with *sulfapyridine*. Benson advised 0.14 gm per kilogram (1 grain per pound) of body weight as the initial dose and then a fourth of this dose four times a day. Lewis also quoted the results with *sulfapyridine* of a New York City group which reported forty-one cures in forty-three cases. Administration of these doses was continued for seven days. The report of Lewis antedated the use of *sulfathiazole* or *sulfadiazine* for gonorrheal infantile vaginitis but Adair and Hac expressed the opinion that their results were as good as *sulfathiazole* as with *sulfapyridine* and that the former drug is less toxic than the latter. Both Lewis and Adair and Hac warned that clinical cure may be present with positive bacteriologic findings. Estrogens may be used when drug-fast vaginitis is encountered, though this is rare except when sulfanilamide is used. Adair and Hac expressed the belief that sulfanilamide is contraindicated in treatment of gonorrheal vaginitis of children, as it produces drug-fast strains frequently. I have not seen any mention of the use of penicillin for this condition but its use should be a welcome therapeutic addition.

**Infections of the Urinary Tract**—After apparently successful treatment of women in or out of the gravid state for urinary infections their subsequent condition should be followed thoroughly to prove unequivocally that they are cured, so as to prevent late but disastrous renal damage. Small doses of *sulfadiazine* or *sulfathiazole*, such as 1 gm three a day, often are sufficient. When chemotherapy fails or if it is

known that the infection is of such a type that sulfonamide compounds are ineffective, acidification with mandelates often is effective. Waugh, McCall and Herrell have shown that chemotherapeutic agents administered intraperitoneally are excreted in effective amounts from the urinary tract for many days. By this means they have reduced materially the incidence of the relatively common infections of the lower part of the urinary tract after gynecologic operations.

**Chancroid**—Kornblith, Jacoby and Chargin<sup>10</sup> stated that 175 cures occurred in a total series of 176 cases of chancroid in an average of two weeks of observation and treatment. Local treatment has worked well when lesions were superficial.

**Pelvic Inflammatory Disease after Radiation**—McKelvey reported the impression from a preliminary evaluation that chemotherapy has much to recommend it in treatment of pelvic inflammatory disease occurring after radiation.

#### PLACENTAL TRANSMISSION

Speert's<sup>23</sup> studies on placental transmission are the most extensive on this subject and he quoted recent literature. He concluded that chemotherapy in pregnancy is relatively innocuous to the fetus unless continued in rather large dosage for considerable time. In the latter case significant jaundice and anemia of the infant have been reported.

#### PENICILLIN

The full therapeutic possibilities and limitations of penicillin are only partially appreciated because of a lack of material for civilian use since ill or wounded members of the armed forces are justly receiving the bulk of the supply of penicillin. Its toxicity is known to be low. Keefer and his associates<sup>1</sup> have reported its use in eight cases of puerperal and postabortal sepsis. Five of these cases were of septic abortion due to anaerobic streptococci. Three patients were reported as recovered or improved and two died. Two patients suffering from staphylococcic puerperal sepsis without bacteremia recovered, as did a patient who had a hemolytic streptococcal postabortal sepsis.

Mitchell and Kamunester<sup>22</sup> reported dramatic results of penicillin therapy in a case of hemolytic streptococcal infection in which the patient was nearly moribund. This patient had repeated positive blood cultures and apparently there was severe pelvic thrombophlebitis of some duration. When the patient became sulfonamide-fast, administration of penicillin was started in doses at first of about 40,000 Oxford units daily. The patient recovered.

The first report to appear on the general subject of penicillin in treatment of sulfonamide resistant Neisserian infections was that by

Herrell, Cook and Thompson<sup>13</sup> Subsequent to this report penicillin has been used at the Mayo Clinic in the treatment of three cases of sulfonamide-resistant gonorrhea of women All three patients were cured One of these patients had had prolonged and adequate chemotherapy with various sulfonamide compounds She had severe gonorrheal proctitis This and other evidences of the Neisserian infection cleared up thoroughly and remarkably in a short time on adequate penicillin therapy This case has been reported elsewhere by Cook, Pool and Herrell<sup>9</sup> Mahoney and his associates<sup>10</sup> have reported success with penicillin in the treatment of seventy-four of seventy-five patients suffering from sulfonamide-resistant gonorrhea These patients were all male

### SULFONAMIDE COMPOUNDS

At present *sulfamerazine* seems to be gaining favor as a chemotherapeutic agent because it appears to be as effective as sulfadiazine and is more soluble and more rapidly absorbed It is excreted more slowly than sulfadiazine Because of these facts smaller doses can be given to obtain proper blood levels which are about the same as for sulfadiazine Sulfamerazine is effective in general against the same organisms as those for which sulfadiazine may be used

The use of sodium bicarbonate to effect an alkaline hydrogen ion concentration of the urine when sulfonamide compounds are administered is usually advised It increases the solubility of the compounds and thereby lessens the danger of urinary complications Brown<sup>4</sup> suggested that 40 grains (2.6 gm) of sodium bicarbonate should be given every four hours

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# PROPHYLACTIC USE OF SULFONAMIDE COMPOUNDS IN THE TREATMENT OF RHEUMATIC FEVER

CHARLES H SLOCUMB AND HOWARD F POLLEY

THE high frequency of tonsillitis and pharyngitis preceding an attack of rheumatic fever has been well established. Repeated cultures have shown that the usual offending organism causing the sore throat belongs to Group A of the hemolytic streptococci. Further studies of patients suffering from acute rheumatic fever by means of antistreptolysins, antifibrinolysins, agglutinins and precipitins suggest that hemolytic streptococcal infections are present or have been present recently. However, sulfanilamide, so useful in many hemolytic streptococcal infections, does not have a similar therapeutic value in the treatment of acute rheumatic fever. In fact it seems to aggravate the symptoms of acute rheumatic fever.<sup>9, 12</sup> It may produce a toxic reaction with a high fever and precipitate congestive heart failure.<sup>5</sup> Even if sulfanilamide is administered as treatment of a hemolytic streptococcal infection of the throat before symptoms of acute rheumatic fever occur, the sulfanilamide does not furnish any protection against the appearance of acute rheumatic fever after this sore throat.<sup>2, 3, 6, 9, 12</sup>

Although sulfanilamide is thus ineffective in the treatment of rheumatic fever, it does have a prophylactic effect. In 1939, Coburn and Moore,<sup>2</sup> and Thomas and France<sup>14</sup> published their studies on the prophylactic administration of sulfanilamide daily during the fall, winter and spring seasons to patients who had had rheumatic fever. When daily administration was carried out, not only were there very markedly fewer attacks of rheumatic fever but also many fewer attacks of hemolytic streptococcal sore throats. Their last reports and reports by others are listed in the tabulation.

It is apparent that sulfanilamide administered in doses of 1 to 3 gm daily is very effective in preventing most flare-ups of rheumatic fever during the time the sulfanilamide is given. The very low frequency of rheumatic fever among the treated patients is apparently due to the marked decrease of the presence of beta hemolytic streptococcal throat infections during treatment. Seven hundred and fifty-one patient-seasons of treatment are reported in the literature. In the group who received treatment there were only twelve patients (1.6 per cent) who had acute rheumatic fever while taking sulfanilamide. In the control groups during the same periods of study recurrences occurred in from ~10 to 45 per cent of those who did not receive sulfanilamide.

## REVIEW OF REPORTED CASES OF THE USE OF SULFANILAMIDE AS A PROPHYLACTIC TREATMENT OF RHEUMATIC FEVER

Authors	Cases in Which Sulfanilamide Was Used				Controls	
	Daily Dose of Sulfanilamide, Grams	Patient Seasons	Results	Toxic Effects	Patient Seasons	Recurrences, Per Cent
Coburn and Moore <sup>2</sup>	2 to 3	184	Excellent 1 flare-up	10 per cent None severe	Large series previously studied	35
Thomas <sup>12</sup>	1 to 1.3	114	Excellent 2 minor attacks	Few and mild	150	10
Stowell and Batton <sup>11</sup>	1.5 to 2	46	2 flare-ups	1 death agranulocytosis 25 per cent stopped treatment because of toxicity		
Hansen, Platon and Dwan <sup>7</sup>	1-3	78	1 recurrence	Seldom	46	45
Fattner and Reyerbach <sup>1</sup>	1-2	108	1 recurrence	15 per cent None serious	104	24
Mendell and Robbins <sup>14</sup>	1.2	25	1 recurrence and 1 case of subacute bacterial endocarditis	None severe 40 per cent mild	30	10
Chandler and Tarsus <sup>1</sup>	0.6 to 1.5	41	1 recurrence	12 per cent stopped treatment because of toxicity 1 patient jaundiced	41	12
Thomas for United States of America <sup>12</sup>		155	3 recurrences			
Id		751	12 recurrences 1 subacute bacterial endocarditis			

## TOXIC REACTIONS

Toxic reactions have occurred in from 10 to 40 per cent of the cases in which sulfanilamide was used and in which definite percentages were stated. In two series toxic symptoms were stated to be, respectively, "few and mild" and "seldom." The reactions include rash, fever, anemia, nausea or a lowering of the white cell count.

When a *rash*, *nausea* or *mild fever* occurs, it may be possible to start administration of sulfanilamide again after intermitting it for a few weeks but if symptoms recur it should be discontinued.

The *lowering of the white cell count* is of most significance. In one case<sup>11</sup> agranulocytosis developed and the patient died as a result of taking 0.6 gm of sulfanilamide three times a day for twenty-eight days. In one other case<sup>7</sup> the number of leukocytes dropped to 1,700 per cubic millimeter of blood with 12 per cent polymorphonuclear cells. The count returned to normal after discontinuance of administration of sulfathiazole, which this patient had been taking. Thomas<sup>12</sup> has observed white blood cell counts as low as 2,000 per cubic millimeter with only 25 to 30 per cent polymorphonuclear leukocytes. In these cases the counts have returned to normal without discontinuance of administration of sulfanilamide. It is safest, however, to make daily counts on patients whose counts are less than 4,000 per cubic millimeter of blood with 45 per cent or less polymorphonuclear leukocytes to be sure that neutrophils will not continue to decrease. If in doubt, administration of sulfanilamide should be discontinued. In most cases in which agranulocytosis develops while the patient is taking sulfanilamide it does so during the first month, mainly during the latter part of the third or during the fourth week. During at least the first month of administration of sulfanilamide the white count should be checked twice a week if the count remains within normal range, thereafter, a count once a week may be adequate. One exceptional case was reported by Hansen, Platou and Dwan<sup>7</sup> in which the leukopenia (1,700 leukocytes in each cubic millimeter of blood) and depression of the proportion of polymorphonuclear cells (12 per cent) occurred during the fifth month of medication. The medication used had been sulfadiazine until a short time before the toxic reaction occurred, when sulfathiazole had been given.

Significant *anemia* is very seldom encountered during the administration of sulfanilamide in doses of 1 to 3 gm daily. Weekly determinations of hemoglobin are advisable, however, during the administration of the drug.

Most investigators have felt that the risk of significant toxicity was sufficiently small to warrant the use of sulfanilamide for prophylaxis

against rheumatic fever Stowell and Button,<sup>11</sup> and Messeloff and Robins<sup>10</sup> were the only ones who discontinued further study because of unfavorable reactions.

#### DOSAGE AND ADMINISTRATION

The amount of sulfanilamide that has been used has varied from 1 to 3 gm daily, divided into three doses Coburn and Moore,<sup>3</sup> used from 2 to 3 gm of sulfanilamide daily Thomas and France<sup>14</sup> gave from 1 to 13 gm daily and obtained equally good protection from recurrences of acute rheumatic fever The levels of sulfanilamide in the blood ranged from 1 to 5.5 mg per 100 cc. of blood. Subsequent workers have used from 1 to 3 gm daily From the information available the smaller doses are as effective as are the larger ones and there are a few instances in which the larger doses produced mild toxic reactions which disappeared when the smaller doses were given

Sulfanilamide usually has been given from October until June This is the period of highest frequency of sore throats and of attacks of acute rheumatic fever Coburn and Moore<sup>4</sup> studied 100 patients over a year's period in 1939 and 1940, by discontinuing the administration of sulfanilamide for a year In thirty-two cases hemolytic streptococcal sore throats developed during the twelve month period and in 40 per cent of these thirty-two cases there were attacks of rheumatic fever Other isolated cases of flare-ups of rheumatic fever when sulfanilamide was not being given during the summer months were reported The prophylactic effect of sulfanilamide does not extend beyond the period during which the medication is being administered. Thomas<sup>15</sup> urged that administration of sulfanilamide be started before the patient leaves the hospital even though the sedimentation rate has not returned to normal after the acute attack of rheumatic fever, provided the patient is completely free from symptoms and fever without administration of salicylates This procedure is urged to protect the patient from reinfection with hemolytic streptococci when he returns home Thomas also expressed the opinion that it would be better to give the sulfanilamide during the entire year in order to avoid the occasional acute attacks of rheumatic fever that occur in the summer The duration of time that sulfanilamide should be given cannot be settled but Thomas<sup>15</sup> advised that it be given for five years after an attack of acute rheumatic fever or if the patient is a child that sulfanilamide be given until he is a young adult.

#### SUMMARY

A review of the literature shows that sulfanilamide has been administered prophylactically through 751 patient-seasons to patients who

have had acute rheumatic fever. In this group of treated patients there were twelve (16 per cent) who had recurrences of acute rheumatic fever or chorea during the period of treatment, as compared with 10 to 45 per cent among controls.

Sulfanilamide is contraindicated in the treatment of acute rheumatic fever and is of no value in preventing a flare-up of rheumatic fever if treatment is started after the hemolytic streptococcal sore throat has developed. However, sulfanilamide in small doses is very effective in preventing recurrent hemolytic sore throats and recurrent attacks of acute rheumatic fever if it is given in daily doses of 1 to 3 gm during the time that there is no activity of rheumatic fever. The beneficial effects of sulfanilamide are present only during the time that it is being taken.

The use of sulfanilamide has focused attention on the prevention of rheumatic fever rather than on the treatment of active rheumatic fever. It is probable that sulfadiazine will be as effective as sulfanilamide and less toxic in the treatment of these patients.

Toxic reactions to sulfanilamide were encountered in 10 to 40 per cent of the cases. Only seldom are the reactions serious. One death from agranulocytosis has been reported. During treatment, frequent determinations of white blood cell counts and differential count, and occasional determinations of hemoglobin and sulfanilamide content of the blood should help minimize the risk of significant reactions. Fever, rash and nausea may necessitate discontinuing administration of sulfanilamide temporarily or permanently.

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## SULFONAMIDE TREATMENT IN DERMATOLOGY INDICATIONS AND LIMITATIONS

LOUIS A. BRUNSTING

THE indications for the use of drugs of the sulfonamide group in the treatment of diseases of the skin have been fairly well established. Although the emphasis in recent dermatologic discussions has been on the topical treatment of pyogenic infections and on the reactions of intolerance to the drugs, it is recognized that the oral route of administration of the sulfonamide drugs fills a need in the management of certain systemic diseases manifested in the skin.

In average dermatologic practice, however, the occasions are few which administration of heroic doses of any of the sulfonamides is justified. Furthermore, the dermatologist now is confronted with an increasing number of cases of untoward reaction to the sulfonamides. Some of these reactions lead to pemphigus-like bullous eruptions or exfoliative dermatitis with prolonged periods of disability and occasionally to a fatal termination. The perspective of the dermatologist concerning the proportion of patients who should be treated by these ubiquitous drugs and the percentage of those who manifest unfavorable reactions, therefore, is likely to be distorted.

Toxic effects or reactions of intolerance may be held at a minimum by proper selection of cases, judicious dosage, careful supervision of the progress of the infection under treatment and periodic examination of the blood and urine. In all cases it is essential to inquire about previous reactions or signs of intolerance. In the treatment of infections of moderate degree, dosage should be held at a minimum. In severe infections, treatment is started with large doses and best results occur when the concentration of the drug in the blood is maintained at a high level. It must be remembered that, even though the sulfonamides are well tolerated on one or more occasions, there is no assurance that untoward reactions will not develop with continued or repeated use. Experience indicates that the highest percentage of reactions occurs with sulfanilamide and that the other commonly used drugs may be listed in the order of decreasing toxicity as follows: sulfathiazole, sulfapyridine, sulfadiazine and sulfamerazine; furthermore, it may be emphasized that sulfamerazine and its acetyl derivative are more soluble than the other drugs mentioned and that after a sizeable initial dose is given, a satisfactory level of concentration in the blood may be



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THE indications for the use of drugs of the sulfonamide group in the treatment of diseases of the skin have been fairly well established.<sup>2</sup> Although the emphasis in recent dermatologic discussions has been on the topical treatment of pyogenic infections and on the reactions of intolerance to the drugs, it is recognized that the oral route of administration of the sulfonamide drugs fills a need in the management of certain systemic diseases manifested in the skin.

In average dermatologic practice, however, the occasions are few in which administration of heroic doses of any of the sulfonamides is justified. Furthermore, the dermatologist now is confronted with an increasing number of cases of untoward reaction to the sulfonamides.<sup>1</sup> Some of these reactions lead to pemphigus-like bullous eruptions or exfoliative dermatitis with prolonged periods of disability and occasionally to a fatal termination. The perspective of the dermatologist concerning the proportion of patients who should be treated by these ubiquitous drugs and the percentage of those who manifest unfavorable reactions, therefore, is likely to be distorted.

Toxic effects or reactions of intolerance may be held at a minimum by proper selection of cases, judicious dosage, careful supervision of the progress of the infection under treatment and periodic examination of the blood and urine. In all cases it is essential to inquire about previous reactions or signs of intolerance. In the treatment of infections of moderate degree, dosage should be held at a minimum. In severe infections, treatment is started with large doses and best results occur when the concentration of the drug in the blood is maintained at a high level. It must be remembered that, even though the sulfonamides are well tolerated on one or more occasions, there is no assurance that untoward reactions will not develop with continued or repeated use. Experience indicates that the highest percentage of reactions occurs with sulfanilamide and that the other commonly used drugs may be listed in the order of decreasing toxicity as follows: sulfathiazole, sulfapyridine, sulfadiazine and sulfamerazine; furthermore, it may be emphasized that sulfamerazine and its acetyl derivative are more soluble than the other drugs mentioned and that after a sizeable initial dose is given, a satisfactory level of concentration in the blood may be

maintained on much lower doses than with either sulfadiazine or sulfathiazole.

#### SULFONAMIDE TREATMENT OF SYSTEMIC DISEASES OF THE SKIN

There is a group of systemic dermatologic diseases without clear-cut bacteriologic definition in which with a few exceptions, therapeutic failure has resulted from use of the sulfonamides. These diseases are pemphigus, erythema multiforme, dermatomyositis, erythema nodosum and disseminated lupus erythematosus. In the field of *nonsyphilitic venereal infections*, namely, chancroid, the early phases of lymphogranuloma venereum and as a part of the treatment of the rare disease, keratoderma blennorrhagicum, the sulfonamides are unexcelled. The administration of the sulfonamides also is of distinct value in *pyogenic infections* of the skin in the acute or chronic and disabling phases, in which the staphylococci are the predominating organisms or when intercurrent bouts are complicated by invading hemolytic streptococci. These pyogenic infections of the skin are erysipelas, cellulitis, lymphangitis, pyoderma, hidradenitis suppurativa and pyoderma gangraenosum. A few instances of widespread infectious eczematoid dermatitis may be included. Set apart from these groups is dermatitis herpetiformis, a chronic, disabling disorder of unknown etiology, which is peculiarly responsive to sulfapyridine but only so long as a small concentration of the drug remains in the circulation.

In cases of *erysipelas*, in which infection is localized, roentgen therapy alone is adequate although ultraviolet irradiation may suffice for infants and young children. If the patient with spreading erysipelas is debilitated or elderly, the prognosis is naturally guarded. In such cases roentgen therapy can be combined with cautious chemotherapy.

In cases of *regional lymphangitis* of the face, ears, genitalia and extremities which are characterized by irregular, recurrent attacks of peculiar violence lymphedema of the member may develop. Lymphangitis of the lower part of the legs is not infrequently a sequel to dermatophytosis of the feet presumably the fissures at the site of the fungous infection are penetrated by hemolytic streptococci. In this group of diseases sulfonamide compounds favorably influence the acute phenomenon and in some instances interrupt the cycle of recurrences.

Occasionally in the presence of several *carbuncles* with systemic reaction, the oral administration of the sulfonamide drugs and the local application of powdered sulfathiazole to the opened wounds have been attended with benefit.

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## SULFONAMIDE TREATMENT IN DERMATOLOGY· INDICATIONS AND LIMITATIONS

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In average dermatologic practice, however, the occasions are few in which administration of heroic doses of any of the sulfonamides is justified Furthermore, the dermatologist now is confronted with an increasing number of cases of untoward reaction to the sulfonamides<sup>1</sup> Some of these reactions lead to pemphigus-like bullous eruptions or exfoliative dermatitis with prolonged periods of disability and occasionally to a fatal termination The perspective of the dermatologist concerning the proportion of patients who should be treated by these ubiquitous drugs and the percentage of those who manifest unfavorable reactions, therefore, is likely to be distorted

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Occasionally in the presence of several *carbuncles* with systemic reaction, the oral administration of the sulfonamide drugs and the local application of powdered sulfathiazole to the opened wounds have been attended with benefit.

*Extensive pyoderma* with multiple lesions on the head and trunk may be a sequence of severe acne and although the chief consideration in

the treatment of such cases is the nutritional status of the patient, the local and systemic administration of the sulfonamide drugs is of value in selected cases

*Hidradenitis suppurativa* is more common than is generally appreciated. Essentially it is a form of pyoderma with predilection for the axillae or genitalia, where the apocrine glands are abundant and active. It may occur by itself or in association with dissecting cellulitis of the neck and scalp or with acne conglobata. The earliest lesions are staphylococcic abscesses and treatment is by drainage or incision aided perhaps by filtered roentgen therapy in moderate dosage. In long-standing cases, sinuses and extensive denudation of the surface may result, complicated by periodic bouts of hemolytic streptococcic lymphangitis. In such instances the best procedure is to administer one of the sulfonamide drugs, such as sulfathiazole or sulfamerazine, in sizeable doses and to unroof the infected sites surgically after the acute phase has subsided.

The cutaneous lesions of *pyoderma gangraenosum* appear to be the development of metastatic abscesses in skin which has become sensitized because of some focal, systemic disability, most frequently ulcerative colitis. More often than not, the abscesses are sterile, or staphylococcic, or a mixture of staphylococci plus hemolytic streptococci is obtained. In such cases the main concern is the general health of the patient and the control of the underlying debilitating disease. In the acute phase, the sulfonamides occasionally may exert benefit but they are poorly tolerated except for azosulfamide and sulfaguanidine, which are relatively nontoxic but also of low therapeutic efficiency. In selected cases, benefit has resulted from the judicious use of these drugs when they have been given for periods of ten to fourteen days out of each month for extended periods of time.

*Dermatitis herpetiformis* responds particularly well to sulfapyridine. During the past four years at the Clinic we have treated fifty-two patients who had this disorder with sulfapyridine. There were fifty adults and two children aged two and four years respectively. Thirty of the adult patients were men and twenty were women. In the case of the adults, the average dose of the drug given by mouth was 3 to 4 gm daily for four or five days, then 2 gm daily for a week, then only as much as was necessary to control the eruption. For the two children the dose was modified according to body weight. The treatment was successful in the case of one child, the other had an uncontrollable recurrence. In more than three-fourths of the cases of adults the discomforts of the eruption were controlled by a maintenance dose of 1 to 2 gm or less of sulfapyridine per day, no new lesions appeared

while a barely appreciable concentration of the drug was present in the circulating blood. In five instances mild reactions of intolerance occurred, in two it was necessary to discontinue administration of the drug. Precautions were taken during treatment to have the patient under medical observation with periodic examinations of the blood and urine. Three of the patients who had the most severe type of dermatitis herpetiformis have been maintained in relative comfort for more than two years on a maintenance dose of 1 to 2 gm of sulfapyridine per day. Because of the occasional tendency of renal calculi to develop during treatment with sulfapyridine if the urine becomes concentrated all patients were admonished to ingest liberal amounts of fluids to the equivalent of 2 to 3 quarts (2,000 to 3,000 cc) daily while under treatment.

The mode of action of sulfapyridine in dermatitis herpetiformis is unknown. Surely there can be little bactericidal effect from such small doses. Presumptive evidence indicates that the disease is a manifestation of hypersensitivity, in which case a small amount of sulfapyridine in the circulation may be sufficient to interfere with the completion of the systemic reaction in the skin.

#### TOPICAL APPLICATION

Sulfathiazole seems to be the most effective drug for topical application and its particular field of usefulness is in impetigo contagiosa, ecthyma, ulcers and wounds which are infected with staphylococci or hemolytic streptococci. A concentration of 5 per cent sulfathiazole in ointment form has proved to be sufficiently strong in most instances of superficial infections, such as impetigo and folliculitis.

The number and variety of brands of proprietary products of this sort which are on the market lead me to fear that the use of the drug may be extended to the treatment of many miscellaneous diseases of the skin by the nondiscriminating. That such fear is justified is attested by the increasing number of cutaneous reactions of sensitivity which are observed by dermatologists. It is not uncommon to see sulfathiazole ointment applied to sites of psoriasis, eczema and stasis ulcers under fixed bandages. In such cases dermatitis often develops in the vicinity of the wound and a systemic reaction of erythema multiforme follows and produces a greater degree of disability than the original condition for which treatment was prescribed. Once sensitivity has been established there may be serious interference with tolerance if the occasion should arise to administer sulfonamides for some intercurrent systemic disease. An unusual reaction of the type came to my attention recently.

A young physician sustained a severe reaction of dermatitis about the face and neck following the application of 25 per cent sulfathiazole ointment for resistant impetigo contagiosa. Two years later because of diarrhea and an upper respiratory infection, he took four 0.5 gm. sulfathiazole tablets by mouth during the course of one day. That evening he noticed swelling of the face and neck and within twenty-four hours pronounced dermatitis venenata was present. This was limited sharply to the sites on the face and neck of previous reaction. In addition, there was mild toxic erythema of the distal portions of the extremities. After a few days of extreme discomfort the reaction subsided and within a period of ten days the skin returned to normal.

Powdered sulfathiazole and sulfanilamide, alone or in combination, are frequently implanted in surgical wounds in the presence of pyogenic infection. Sulfathiazole in combination with urea<sup>3</sup> is of particular merit in the cleansing of deep and undermining burrowing ulcers which are infected by hemolytic streptococci.

In certain painful ulcerative conditions of the mouth, such as extensive aphthae, or in some cases of pemphigus or erythema multiforme, I have observed soothing and antiseptic effects from a mouth wash consisting of 5 per cent aqueous solution of sodium sulfathiazole. Caution should be exercised in the long-continued use of this chemical, for reactions of intolerance occasionally develop following the absorption of the drug from the sites of ulceration.

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# THE USE OF TYROTHRICIN IN THE TREATMENT OF ULCERS OF THE EXTREMITIES DUE TO PERIPHERAL VASCULAR DISEASE

WALTER F. KVALE, NELSON W. BARKER AND WALLACE E. HERRELL

Dubos<sup>1</sup> in 1939 reported his studies of the isolation of an antibacterial substance of biologic origin. The crude substance which he isolated was given the name gramicidin, since the material was definitely antibacterial for gram-positive pathogenic bacteria. This substance may be isolated from cultures of an anaerobic sporulating soil bacillus (*Bacillus brevis*). It was subsequently found that the crude material, now known as tyrothricin, contains two substances, gramicidin and tyrocidine. It also has been shown that the tyrocidine fraction of tyrothricin is to some degree inhibitory for certain gram-negative pathogens. Both fractions of tyrothricin have been found to be complex polypeptides. These polypeptides are high in nitrogen content.

Neither gramicidin nor tyrocidine has been synthesized. However, the amount of tyrothricin obtainable from the broth cultures of *Bacillus brevis* is fairly large. From 1 liter of culture of *Bacillus brevis* at times 500 mg. or more of tyrothricin may be obtained. Although different batches of tyrothricin may vary, as a rule the mixture contains approximately 50 per cent tyrocidine and 20 per cent gramicidin. Since the yield from the broth filtrate is fairly high, it does not appear necessary to attempt to synthesize either of the fractions of tyrothricin.

Data are not yet complete concerning the size of the molecule of either gramicidin or tyrocidine. Dubos and Hotchkiss,<sup>2</sup> however, have proposed a satisfactory empirical formula for gramicidin  $C_{74}H_{105}N_{15}O_{13}$  (mol. wt. 1,413). They have also pointed out that tyrocidine is a basic polypeptide. In contrast to gramicidin, tyrocidine according to Dubos and Hotchkiss contains many amino acids. As the result of preliminary studies, the approximate formula suggested for tyrocidine is  $C_{126}H_{166}N_{26}O_{26} \cdot 2HCl$  (mol. wt. 2,534).

It has been shown repeatedly that tyrothricin is relatively free from any serious toxic effects for tissue with the exception of its hemolytic effect on the erythrocytes in the blood of experimental animals as well as in the blood of human beings. Heilman and one of us<sup>3</sup> have studied the hemolytic effect of both fractions of tyrothricin, but, nevertheless, all attempts to remove the hemolytic property of gramicidin have re-



sulted also in a loss of its bacteriostatic action Tyrothricin, therefore, in spite of its high degree of antibacterial activity, must be limited to local treatment alone

Heilman and one of us<sup>4</sup> further studied the cytotoxicity of gramicidin and tyrocidine as well as of other bactericidal agents It was found that gramicidin is more toxic than tyrocidine for cells migrating from explants of mammalian lymph node Nevertheless, the amount of gramicidin necessary to produce any appreciable toxic effect was large as compared with the amount necessary to kill most gram-positive cocci As a result of the tissue culture studies just mentioned, evidence was presented to indicate that it is probably not desirable to fractionate tyrothricin for clinical use Since gramicidin is more cytotoxic than tyrocidine, there would be little advantage in using purified gramicidin for the purpose of avoiding toxicity Tyrocidine, furthermore, aids in keeping gramicidin in suspension and also inhibits gram-negative bacteria, on which gramicidin is said to have little effect Further studies by Heilman, Gage and one of us<sup>6</sup> and by Heilman and one of us<sup>5</sup> would indicate that the cytotoxicity of tyrothricin is, indeed, very low as compared with that of a number of other germicides suitable for local treatment Gramicidin produced less toxicity for tissue than any of the other germicides studied with the exception of penicillin

The antibacterial activity of the anionic detergent-like substance, gramicidin, can be neutralized by cationic detergents, such as phemerol The simultaneous use of gramicidin and a cationic detergent in the treatment of infections is contraindicated There is no contraindication, however, to the simultaneous use of gramicidin with anionic detergents, including the ordinary soaps

#### CLINICAL OBSERVATIONS

**Ulcer Types in Peripheral Vascular Disease**—In the treatment of patients suffering from peripheral vascular disease two types of ulcers are encountered The first type is the so-called *venous stasis ulcer*, which results primarily from chronic venous insufficiency of the leg The venous insufficiency is the result either of previous thrombophlebitis or of primary varicose veins of long standing Ulcers of the leg may develop in cases of chronic venous insufficiency after gross mechanical trauma, sometimes of only mild degree, after burns and after local infection of the skin They may also develop in areas of indurated cellulitis and in areas of eczema Occasionally the ulcer develops spontaneously without any of the before-mentioned precipitating factors The ulcers are located most commonly in the region of the malleoli,

particularly just proximal to them and more commonly on the mesial than on the lateral side. They may be single or multiple and may vary greatly in size. Ulcers more than 15 cm in diameter are encountered occasionally. Once developed, venous stasis ulcers usually become secondarily infected, although the virulence of the infecting organism is usually low. They usually become chronic and indolent and may persist for years. Factors which inhibit healing are local edema and congestion, infection and sometimes the injudicious use of irritating external applications.

In the treatment of large or indolent venous stasis ulcers the first principle is to relieve the congestion and edema by putting the patient to bed with the affected leg elevated. The second principle is to avoid the use of any local application which is even slightly irritating to tissue. Many local applications have been used successfully, and it has been stated that venous stasis ulcers will heal, regardless of what local application is used if the patient is in bed with the leg elevated. This is not entirely true and it may be weeks or months before large ulcers heal. The ideal local application is one that is absolutely non-irritating, is bactericidal or bacteriostatic (to combat the secondary infection) and will stimulate the formation of granulation tissue and the growth of epithelium. The use of such a local application may greatly shorten the period of disability. In cases of very large ulcers it will also prepare a good bed for a skin graft if a graft is thought advisable.

The second type of ulcer encountered in the treatment of peripheral vascular disease is the *ischemic ulcer*. Such ulcers occur in cases of occlusive arterial disease, either thrombo-angitis obliterans or arteriosclerosis obliterans. They are usually located on the digits, more rarely on the foot or lower part of the leg. They may develop spontaneously or following minor trauma, infection, burns or frostbite. A chronic indolent ulcer may persist after an area of dry cutaneous gangrene has sloughed, after a digit has been amputated or after a gangrenous digit has sloughed spontaneously. The arterial blood supply at the base of these ulcers is poor, therefore, oxygenation and nutrition of the cells are deficient. Ischemic ulcers are always secondarily infected and this factor delays healing and may cause extension of necrosis of skin. Granulation tissue develops slowly, if at all. The ulcer may be painful and cause prolonged disability.

Diabetes mellitus may be present in cases in which there are arteriosclerosis obliterans and ischemic ulcers. In such cases the resistance of tissues to infection, particularly by staphylococci and streptococci is poorer than when diabetes is not present. The capacity for healing of ischemic ulcers is poor among elderly people. In general it is better if

the underlying disease is thrombo-angitis obliterans than if it is arteriosclerosis obliterans. It is better if the ulcer follows trauma than when the ulcer has developed spontaneously. The problem of healing ischemic ulcers is always difficult and is definitely more difficult than the problem of healing ulcers resulting from venous stasis. There are many procedures whose purpose is to improve arterial blood supply, and these may be partially effective, but it is usually impossible to restore the circulation entirely to normal. The ideal local application for ischemic ulcer is again one that is nonirritating, because the slightest degree of irritation of cells may cause more necrosis and enlarge the ulcer. The application should be bactericidal and bacteriostatic and should stimulate the formation of granulation tissue and the growth of epithelium. Many different local applications have been used to treat ischemic ulcer. Most of them have been discarded because they have been found to be irritating or have failed to produce any effect.

**The Use of Tyrothricin in Treatment**—Because of the very low cytotoxic effect of tyrothricin and its relatively high antibacterial activity, it seemed reasonable to assume that this germicide should lend itself well for the treatment of infected ulcers, especially in those cases in which low toxicity for tissue is exceedingly desirable. Ulcers associated with an impaired vascular apparatus are notoriously susceptible to even slightly cytotoxic agents.

Tyrothricin is relatively insoluble in water but suitable suspensions of the material may be prepared for clinical use by adding an alcoholic solution of tyrothricin or an alcohol-glycerin base of tyrothricin to triple distilled water. The most satisfactory preparation for clinical purposes is that final suspension in distilled water which contains 0.5 gm of tyrothricin per liter (500 micrograms per cubic centimeter).

Solutions were always discarded at the end of ten days and usually at the end of seven days. The solution was applied to the ulcer as a continuous wet dressing. In the case of small ulcers a sterile cotton pad which barely overlapped the margins of the ulcer was saturated with the solution and applied directly to the ulcer. This pad was moistened with the solution every hour by means of a medicine dropper. The pads were changed at least every twenty-four hours and oftener if there was much discharge from the ulcer. In the case of large ulcers large cotton pads were used and covered with oiled silk. The pads were moistened before being applied and were allowed to overlap the margin of the ulcer only slightly. Occasionally some of the cotton adhered to the base of the ulcer but this was disregarded when a new pad was applied. Occasionally such adherent cotton was removed gently with forceps.

TABLE 1—RESULTS OF TREATMENT WITH TYROTHRICIN IN CASES OF VENOUS STASIS ULCERS

Case	Sex	Age years	Site and Location of Ulcer	Type of Treatment	Duration of Treatment	Comment	Results
1	M	55	Ulcers anterior surfaces both legs	Tyrothricin	7 days in hospital, 1 month at home	Ulcer almost healed in hospital, ulcer healed completely at home	Good
2	M	46	Ulcer 3 by 3 cm. external aspect left leg	Tyrothricin	6 days	50% healing during short period	Good
3	M	35	Ulcer 4 by 4 cm. above left internal malleolus	Tyrothricin	2½ weeks	Healed	Good
4	M	32	Multiple small stasis ulcers right ankle	Tyrothricin	10 days	Healed	Good
5	F	30	Ulcer 5 by 5 cm. lateral surface junction middle and lower thirds left leg with surrounding cellulitis	Elevation and packs of 1% aluminum subacetate for 7 days until cellulitis had subsided. Tyrothricin thereafter	Tyrothricin for 30 days	Healed	Good
6	F	37	Ulcer 6 by 6 cm. right leg 6 years duration	Sulfacilamide by mouth one week. Tyrothricin	25 days	Healed	Good
7	M	51	Ulcer 2.5 by 2.5 cm. over right internal malleolus	Tyrothricin	29 days	Healed	Good
8	F	54	3 ulcers 1 to 2 cm. in diameter left leg	Tyrothricin	14 days	Healed	Good
9	M	39	2 deep boggy ulcers lateral surface left leg	Tyrothricin	11 days	Ulcers 25% healed	Fair
10	M	35	2 large and 1 small ulcer left leg	Tyrothricin	10 days	Skin grafts eventually necessary	Fair
11	F	70	Ulcer 3 by 1 cm. medial surface left leg	Tyrothricin	1 month together with sulfathiazole ointment and aluminum subacetate packs	Ulcer partially healed on tyrothricin	Fair
12	M	47	Recurrent stasis ulcer 2 by 2.5 cm. medial surface left ankle	Aluminum subacetate packs for 15 days. Tyrothricin for 25 days	38 days total	No change after 13 days' treatment with aluminum subacetate. 90% healed after 25 days with tyrothricin	Fair
13	F	48	Large ulcer left leg	Tyrothricin	13 days	30% healed and clean	Fair
14	F	59	Large deep infected ulcer and one small ulcer left leg	Tyrothricin	14 days	20% healed and clean. Ulcer later healed at home with sulfathiazole ointment and rest in bed	Fair
15	M	65	4 stasis ulcers 1 to 3 cm. in area of external malleolus	Tyrothricin	10 days	Ulcers 50% healed	Fair

TABLE 2—RESULTS OF TREATMENT WITH TYROTHRICIN IN CASES OF ISCHEMIC ULCER ASSOCIATED WITH THROMBO-ANGIITIS OBLITERANS

Case	Sex	Age Years	Size and Location of Lesion	Type of Treatment	Duration of Treatment	Comment	Results
1	M	51	Ulcer L 1 toe Large necrotic ulcer left calf	One injection typhoid vaccine Sander's bed Tyrothricin	30 days	Ulcer L 1 toe healed Ulcer left calf 50% healed	Good
2	M	50	Ulcers R 2, 3, 4 fingers	Tyrothricin Cervicothoracic sympathectomy	28 days	Ulcers healed	Fair
3	M	37	Large gangrenous ulcer at site of previously amputated R 2 toe and mass gangrene R 3 toe	Injections of typhoid vaccine. Tyrothricin	51 days	Ulcer base R 2 toe 30% healed R 3 toe then amputated Tyrothricin continued with entire ulcer healed in 1 month	Good
4	M	41	Necrotic ulcer L 1 toe Small ulcer lateral aspect left foot	Injections of typhoid vaccine Sander's bed. Tyrothricin	10 days with tyrothricin	No results after 10 days' treatment with tyrothricin Thereafter with sulfathiazole ointment Ulcer 95% healed in 6 weeks	Failure
5	M	33	Ulcer nail bed L 1 toe	Injections of typhoid vaccine. Sander's bed Tyrothricin	30 days	Dismissed with ulcer painless but still unhealed	Fair
6	M	44	Large ulcer lateral aspect right foot with osteomyelitis base R 5 metatarsal	Ulcer and sinus curetted with drainage persisting for 28 days Tyrothricin then started	15 days	Ulcer and sinus healed	Good
7	M	52	Small open lesion site of amputated stump left leg	Tyrothricin	30 days	Nonhealing of lesion Subsequent excision of ulcerated area	Failure
8	M	47	Ulcers dorsum both first toes L 2, and R 3	Tyrothricin	47 days	All lesions practically healed	Good
9	M	49	Ulcers L 4 and 5 fingers and gangrene R 4 finger	Tyrothricin	21 days	Ulcers L 4 and 5 fingers healed Amputation R 4 finger	Fair
10	M	27	Ulcers dorsum base L 1 and 2 toes and over L 5 metatarsal head	Tyrothricin intermittently Typhoid vaccine. Sander's bed Lumbar sympathectomy	Total 2 months	Eventual spread of ulcerations to gangrene of left leg and amputation	Failure
11	M	37	Ulcer R 1 toe	Tyrothricin	11 days	Ulcer not healed	Failure
12	M	55	Large gangrenous ulcer R 1 toe	Tyrothricin intermittently Sander's bed Typhoid vaccine. Powdered red blood cells Sulfathiazole ointment	4 months	Nonhealing of ulcer Eventual amputation of leg	Failure

Case	Sex	Age Years	Diabetes Mellitus	Site and Location of Ulcer	Type of Treatment	Duration of Treatment	Comment	Results
1	F	45	Yes	Ulcer 4 by 4 cm. right anterior tibial region. Stasis as well as ischemic	Tyrothricin	45 days	Ulcer healed	Good
2	M	60	Yes	Gangrenous ulcer L 1 toe	Tyrothricin	54 days	Ulcer 50% healed	Fair
3	F	69	Yes	Large gangrenous ulcers lateral and medial surfaces left foot	Tyrothricin	57 days	General opinion that ulcers would not heal. After 57 days treatment ulcers unquestionably healing	Good
4	F	80	No	Gangrenous ulcer ball R 1 nail bed Small ulcer over R 2 midphalangeal joint	Tyrothricin	13 days	Ulcer R 1 toe healed. Nonhealing ulcer R 2 toe	Fair
5	M	54	No	Soughling infected ulcer stump of amputated R 3 toe with edema and cellulitis dorsum of foot	Elevation, scales for 9 days. Tyrothricin thereafter for 41 days	Total 50 days	Ulcer healed	Good
6	M	59	Yes	Gangrenous ulcer L 1 toe	Tyrothricin	3 weeks	Ulcer healing	Fair
7	M	71	No	Nonhealing ulcer site of amputated R 2 toe	Tyrothricin	7 days	Ulcer healed	Good
8	M	67	No	Gangrenous ulcer base medial side nail R 1 toe	Tyrothricin	15 days	Ulcer healed	Good
9	M	56	No	Ulcer site of amputated R 5 toe	Tyrothricin	3 weeks	Ulcer 98% healed	Good
10	M	60	No	Ulcer site of amputated L 1 toe	Sander a bed. Tyrothricin	11 days	Relief of pain, ulcer became cleaner but base of ulcer was head of meta tarsal	Failure
11	M	76	No	Infected fissure between L 4 and 5 toe	Tyrothricin	14 days	Nonhealing of lesion	Failure
12	M	58	No	Gangrene dorsum of right foot	Tyrothricin	10 days	Spread of gangrene. Patient died of mesenteric thrombosis	Failure
13	F	73	No	Infected gangrene R 1 toe	Tyrothricin	11 days	Progression of gangrene. Eventual amputation of leg	Failure
14	F	56	No	Infected ulcer right leg	Tyrothricin	14 days	Progression in size of ulcer. Eventual amputation of leg	Failure
15	M	62	Yes	Deep 1 by 1 cm. ulcer base L 5 meta tarsal	Tyrothricin. Debridement	1 month	25% healing after 1 month in hospital. 90% healed after 1 more month's treatment at home	Good

**Results**—The clinical results in fifty cases in which ulcers associated with peripheral vascular disease were treated with tyrothricin have been grouped into three tables (1) venous stasis ulcers (Table 1), (2) ischemic ulcers associated with thrombo-angitis obliterans (Table 2) and (3) ischemic ulcers associated with arteriosclerosis obliterans (Table 3) The results in general have been graded as good when the ulcer healed completely or showed evidence of rapid healing in a short period, fair when some healing occurred but healing was incomplete during a prolonged period, and failure when no healing was noted

The fact that the results can be considered good in many of the cases does not necessarily imply that the tyrothricin alone was responsible for the favorable result As a matter of fact, there is no question but that some of these ulcers might have healed with many of the other standard forms of treatment Yet, there is likewise no question but that the ulcers healed much more rapidly with the use of tyrothricin than without its use

On the other hand, the fact that many of the results could be considered as failures is not due entirely to the ineffectiveness of tyrothricin In general it will be noted that the poor results occurred in those cases in which ischemic ulcers were associated with the occlusive arterial diseases The arterial blood supply at the base of these ulcers is very poor and no bacteriostatic agent will cause an ulcer to heal if the arterial insufficiency is so great as to prevent adequate oxygenation and nutrition to the adjacent tissues It is generally not difficult to predict by appropriate and thorough examination of the peripheral arterial tree whether healing of an ischemic ulcer will take place or not These predictions are not always accurate but they are accurate in a large percentage of cases Much depends upon the degree of arterial insufficiency present Many such lesions have healed after long periods of treatment without the use of tyrothricin Since the advent of tyrothricin, however, it has been the general consensus of physicians experienced in treating ischemic ulcers, especially those secondarily infected, that healing has probably occurred more rapidly with the use of tyrothricin than without its use We realize that there are no statistics to support such a statement, yet the results have been so striking in a number of cases that such comment seems justified For instance, in one case (Case 3, Table 3) it was the general opinion that two large gangrenous ulcers on either side of the left foot would not heal and that amputation of the limb should be performed The patient refused amputation and, after fifty-seven days of treatment with tyrothricin, the ulcers were unquestionably healing

Good or fair results were obtained much more frequently in cases of venous stasis ulcers than in cases of ischemic ulcers. Sufficient arterial circulation supplying nutritional needs to the involved tissues is unquestionably responsible in large part for the greater number of good or fair results in these cases than in cases of ischemic ulcers. Out of a total of fifteen cases, good results were obtained in eight cases and fair results in seven. In no case was the result considered to be a failure. In some cases the initial treatment consisted of the application of packs saturated with aluminum subacetate to those ulcers around which there was severe indurated cellulitis. After the cellulitis had subsided tyrothricin was applied to the ulcer itself according to the method already described. The rapid appearance of granulation tissue in the ulcerated area was frequently the first and most striking result. Fairly often it was necessary to cauterize these exuberant granulations with silver nitrate, for frequently the granulations overlapped the margins of the ulcer and, had they been allowed to remain, they might possibly have interfered with healing. In cases of shallow ulcers the granulations often rose above the level of the skin surrounding the ulcer and again required cauterization. Tyrothricin was often withheld for a day or two before being applied again and during this time the ulcer was allowed to remain exposed to the air. By this means—that is, cauterization of the granulations with silver nitrate as needed and the exposure of the ulcer to the air—healing occurred frequently in a relatively short period. The following is an illustration (Case 5, Table 1).

The patient, a white woman, aged thirty years, entered the Clinic June 30 1943, complaining of an ulcer on the lateral surface of the left leg. She gave a history of having had postpartum bilateral iliofemoral thrombophlebitis four years previously followed by the appearance of several ulcers about both ankles, all of which healed spontaneously in a few months. The present ulcer, however, had failed to heal in a year's time despite the use of many local measures. On examination, a superficial ulcer 5 by 5 cm., was observed on the lateral surface of the left leg at the juncture of the middle and lower thirds. There was a surrounding zone of cellulitis and induration. The patient was hospitalized and for the first seven days her leg was elevated and continuous wet packs of 1 per cent solution of aluminum subacetate were applied. At the end of this time the cellulitis had subsided sufficiently so that it was considered advisable to discontinue the wet packs. Thereafter tyrothricin was applied. Granulations rapidly appeared and during the course of the next thirty days silver nitrate was applied to the granulations when considered necessary and the ulcer was exposed intermittently to the air and saturated with tyrothricin. The ulcer gradually healed completely.

Mention has already been made of the reasons for the generally poor results in treating ulcers of ischemic origin. The results are given in Tables 2 and 3. Of twelve cases of thrombo angitis obliterans or —



results were obtained in only four cases, fair results in three cases, and in five cases the result was considered to be a total failure. Of fifteen cases of arteriosclerosis obliterans, good results were obtained in seven cases, fair results in three cases and in five cases the result was considered to be a failure. Failure to obtain fair or good results does not imply that tyrothricin alone was at fault. These are cases in which the arterial blood supply is very poor, and no local medication will effect healing in the face of a blood supply which cannot adequately meet the nutritional needs of the surrounding tissues. Conversely, neither do the good results imply that tyrothricin was responsible for the healing. These may have been lesions in which other local medications might have effected a cure. To prove one and to prove the other are equally impossible. Nevertheless, such good results as were obtained in the following case (Case 3, Table 2) deserve special mention.

The patient, a man, aged thirty-seven years, entered the Clinic October 13, 1942, complaining of a painful ulcer at the site of a previously amputated right second toe and gangrene of the right third toe. His symptoms had begun in 1936 with recurrent bouts of superficial phlebitis involving the lower part of his legs and ankles and followed by intermittent claudication of his arches at two to three blocks in 1939. In 1941 the left first toe had become gangrenous and had been amputated one month later, healing occurring two months later. In June, 1942, his right second toe became gangrenous, sloughed off gradually and was amputated several weeks later. The site of the amputated right second toe did not heal and in August, 1942, the right third toe became gangrenous. On examination, normal pulsations in both radial, ulnar and femoral arteries, decreased pulsations in both popliteal arteries, and absent pulsations in both dorsalis pedis and posterior tibial arteries were observed. Moderate arterial insufficiency was present, as manifested by pallor of the lower extremities on elevation and rubor and delayed venous filling on dependency. The left first toe had been amputated previously and the wound was well healed. The right second toe had been amputated, leaving a large gangrenous ulcer extending upon the dorsum of the foot and into the right third toe, which was completely gangrenous. The right foot was moderately edematous. The diagnosis was thrombo-angitis obliterans. The patient was hospitalized, advised to stop smoking, given injections of typhoid vaccine and given sedatives as necessary to control his pain. Tyrothricin was applied to the ulcer. After three weeks' treatment his pain was 95 per cent relieved and the ulcer had healed 50 per cent. The right third toe was then amputated and after one more month's treatment the ulcer was completely healed.

#### SUMMARY

The clinical results of the use of tyrothricin in the treatment of ulcers associated with peripheral vascular disease indicate that tyrothricin is of definite value in treating certain types of ulcers of both ischemic and stasis origin. Results were generally better in cases of stasis ulcer than in cases of ischemic ulcer.

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## PENICILLIN IN THE TREATMENT OF STAPHYLOCOCCIC SEPSIS

DONALD R. NICHOLS AND WALLACE E. HERRELL

EXTENSIVE staphylococcic cellulitis and staphylococcic cellulitis with bacteriemia have always been considered rather serious infections. Before the modern era of chemotherapy, persons fifty years of age or older who became victims of staphylococcic septicemia had approximately one chance in ten to recover. Mortality statistics gathered from large series of cases of staphylococcic septicemia in which the patients were fifty years of age or older showed a mortality rate of approximately 90 per cent. After the introduction of sulfonamide therapy, mortality rates as low as 30 to 35 per cent were reported by some investigators. In other words, in cases of staphylococcic sepsis in which adequate sulfonamide therapy was employed the mortality rate was reduced from 90 to 30 or 35 per cent. Experience further has indicated that in order to obtain such a low mortality rate one must be certain that the concentration of the sulfonamide in the blood is between 16 and 20 mg per 100 cc. Unless such a concentration is maintained, the mortality rates in general will be no lower than those observed before the advent of sulfonamide therapy. It may be difficult at times to maintain an adequate concentration of the sulfonamide, and such a high concentration is not without certain well-recognized complications.

After the introduction of the highly antibacterial substance, penicillin, it seemed reasonable to assume that even better results could be obtained in the treatment of staphylococcic sepsis. Compared with the sulfonamides, penicillin is exceedingly more antibacterial for most of the strains of staphylococci, and at the same time it appears to be relatively free of any serious toxic manifestations.

Because of the limited supplies of penicillin available, its use in the treatment of staphylococcic sepsis has, for the most part, been limited to those cases in which previous sulfonamide therapy had failed. The results have not been universally satisfactory, but it seems likely that, with the anticipated increase in the supply of penicillin, it may not be necessary to await sulfonamide failure before instituting penicillin therapy. When this becomes possible, it does not seem unreasonable to assume that far better results can be obtained. Any delay, regardless of trial with sulfonamide therapy or other measures, increases the hazard to the patient suffering from staphylococcic sepsis.

For the past two years we have undertaken experimental and clinical studies on the effectiveness of penicillin against a large variety of bacterial infections including staphylococcic sepsis. Although the number of cases of staphylococcic septicemia is not large, we were able to treat in one group fourteen patients of whom twelve recovered. In the two cases in which the patients failed to recover, sulfonamide therapy had been tried and both patients had evidence of valvular heart lesions at the time the administration of penicillin was started. This complication, in our experience, has not developed under adequate penicillin therapy. When such a complication develops, the prognosis is universally poor because the focus of infection cannot be eradicated. In the present clinic on the treatment of staphylococcic sepsis, we are presenting two cases of severe staphylococcic septicemia associated with extensive cellulitis and complicated by pneumonia. Pneumonia is not infrequently seen in association with severe staphylococcic bacteremia. The cases illustrate the problems involved in the successful use of penicillin in the treatment of staphylococcic sepsis.

#### REPORT OF CASES

**Case I.**—The patient was a white man seventy five years of age. He was admitted to the hospital on March 20 1943, because of extensive cellulitis which involved the nose and entire left side of the face. Ten days previously a rather severe infection of the upper part of the respiratory tract had developed. Three days later (seven days before his admission) a furuncle had developed on the septum of his nose. The furuncle had become exceedingly tender and had spread. Three days before his admission, cellulitis had developed in the nose and had involved the upper lid and the left side of the face. The cellulitis subsequently had involved the entire left side of the face and was spreading into the tissues of the neck. The left eye was swollen shut. On the day of his admission the patient had a chill which was followed by a rather sudden rise in his temperature to 104° F. During the initial phases of the infection, adequate doses of sulfathiazole had been administered.

When he was admitted to the hospital, physical examination revealed the furuncle on the nasal septum. There were redness and induration of the upper lip, the left side of the nose and the left cheek. The eyelids on the left side were markedly swollen and edematous. The edema had spread into the tissues of the neck. There was purulent drainage from both sides of the nose (Fig 66, a). At the time of his admission, the oral temperature was 100.6° F and the pulse rate was 96 beats per minute. The leukocyte count was 13 700 per cubic millimeter of blood. In spite of the administration of adequate doses of sulfathiazole, the concentration of the drug in the blood was 5.4 mg per 100 cc. Blood cultures obtained at this time subsequently revealed ten colonies of *Staphylococcus aureus* per cubic centimeter. Hour by hour the patient's condition grew worse. Four hours after his admission the rectal temperature was 106° F., although he was still rational. At this time he complained of pain in the left side of the thorax. Physical examination of the thorax revealed evidence of bilateral pneu-

monia, and roentgenograms confirmed the physical findings (Fig 67, *a*) The patient's condition subsequently became very critical He was semicomatose and

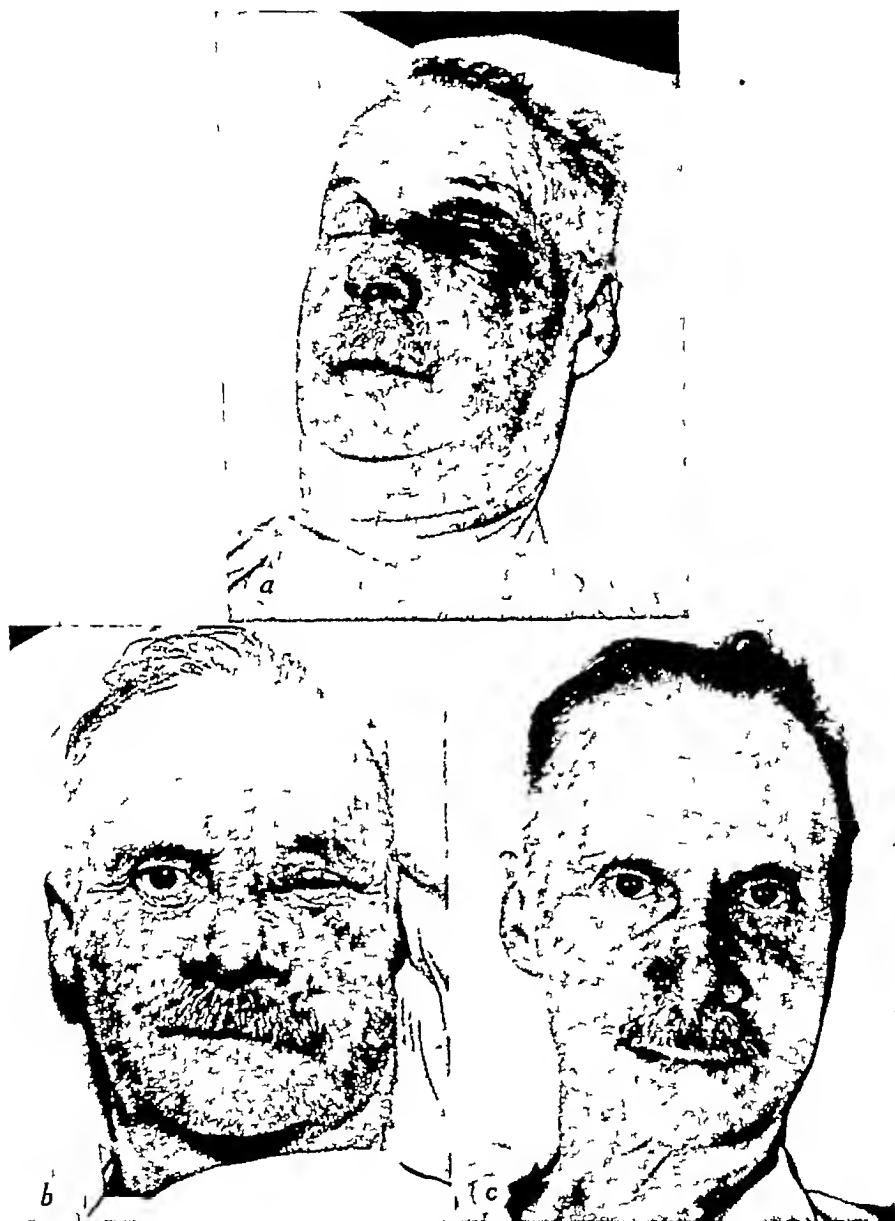


Fig 66—*a*, Appearance of patient in Case I at the time of admission to hospital, one can note extensive nasal and facial cellulitis, severe edema of eyelids and edema extending into the tissues of the neck, *b*, appearance of patient after five days of treatment, *c*, photograph of patient on the tenth day of treatment

the rectal temperature remained between 103° and 104° F At this time the administration of sulfathiazole was discontinued and penicillin therapy was instituted



Fig 67—2, Extensive pneumonia in Case 1 *b*, roentgenographic appearance of lungs after completion of penicillin therapy

The sodium salt of penicillin was administered by the continuous intravenous drip method, which has been described previously<sup>1, 2</sup> Sixteen thousand Oxford units of sodium penicillin dissolved in 1 liter of physiologic salt solution was given every twelve hours The total daily dose was 32,000 Oxford units Penicillin therapy was continued in this fashion for twelve days The patient's general condition improved rather dramatically during the next forty-eight hours of treatment The temperature subsided gradually, which is usually characteristic in cases of sepsis in which penicillin is used. As is frequently seen when penicillin therapy is used, the edema of the soft tissues subsided rapidly After this treatment had been continued for forty-eight hours, blood cultures still revealed a few staphylococci, however, cultures that were obtained subsequently failed to reveal any organisms Improvement continued and the edema of the soft parts was practically gone on the fifth day of treatment (Fig 66, *b*) The leukocyte count at this time was 8,600 per cubic millimeter of blood By the tenth day, the appearance of the patient's face was practically normal (Fig 66, *c*)

During the course of penicillin therapy there was evidence of improvement in the physical findings in the thorax However, a pleural effusion developed on the left side and was slowly absorbed spontaneously No other treatment was employed except oxygen therapy, which was continued during the first five days of the illness Because of the pleural effusion which subsided spontaneously, it was necessary to keep the patient in the hospital for a total of twenty-two days Penicillin therapy, however, was continued for only twelve days At the time of his dismissal on the twenty-second day, the cellulitis of the face had subsided entirely There were no physical findings on examination of the thorax. A roentgenogram of the thorax is shown in Figure 67, *b* There were no toxic manifestations whatever associated with penicillin therapy administered in the manner described

The second case is that of a patient also over fifty years of age who had extensive cellulitis of the arm which was complicated by staphylococcic septicemia and pneumonia This patient also had failed to respond satisfactorily to sulfonamide therapy

CASE II—The patient was a white woman, fifty-seven years of age She was admitted to the hospital on March 28, 1943, suffering from extensive cellulitis of the left forearm The cellulitis had developed subsequent to a furuncle in the region of the left elbow When the patient was admitted to the hospital she was very ill The lesion resembled a huge carbuncle The oral temperature was 102.4° F and the pulse rate was 110 beats per minute The cellulitis involved the greater portion of the left forearm and elbow The axillary lymph nodes were not palpable The leukocyte count was 13,300 Urinalysis revealed a moderate amount of albumin, a few hyaline and granular casts, a few erythrocytes and an occasional leukocyte Blood cultures revealed the presence of 100 colonies of *Staphylococcus aureus* per cubic centimeter of blood Initial treatment consisted of the administration of 15 grains (1 gm) of sulfathiazole every four hours Hot packs were applied to the left arm The following day roentgen therapy was applied to the infected region. Forty-eight hours after admission, in spite of this treatment, the patient was still seriously ill Her temperature continued to rise daily to 102° F Administration of sulfathiazole was discontinued and penicillin therapy



Fig 68.—*a* Extensive bilateral bronchopneumonia (more marked on the right side) in Case II *b*, roentgenographic appearance of lungs after complete penicillin therapy



was instituted by the continuous intravenous drip method. At the time penicillin therapy was instituted, blood cultures still revealed the presence of *Staphylococcus aureus*. The patient was given 16,000 Oxford units of the sodium salt of penicillin in 1 liter of physiologic salt solution twice daily. This was administered at the rate of 30 drops per minute.

On her fourth day in the hospital, the patient complained of pain in the right side of the thorax. Physical examination revealed signs suggestive of bilateral pneumonia. Roentgenographic examination of the thorax disclosed extensive bilateral bronchopneumonia which was somewhat more extensive on the right side (Fig 68, *a*). Oxygen was administered by means of a mask. In spite of the complicating pneumonia, there was marked improvement in the cellulitis of the arm. Blood cultures obtained forty-eight hours after the institution of penicillin therapy revealed the presence of a few colonies of *Staphylococcus aureus*. Blood cultures taken seventy-two hours after the beginning of treatment were negative. The blood cultures remained negative throughout the convalescence. The patient received a total of 232,000 Oxford units of penicillin in seven days. The extensive cellulitis of the left arm became localized forty-eight hours after penicillin therapy was instituted. A few fluctuant regions were present, and these were incised. Thereafter the patient improved steadily, the blood cultures remained negative, and the pneumonia slowly resolved. A small pleural effusion developed on the right side but was absorbed without any interference. Roentgenograms made at intervals revealed small areas of increased density in both lung fields, but these disappeared and the last roentgenograms revealed only a few localized areas of fibrosis (Fig 68, *b*). The total period of hospitalization was seventeen days, and penicillin was administered for seven days. At the time of the patient's dismissal from the hospital, her arm was healed completely.

A very interesting situation developed, with regard to the patient's urinary findings. While she still was receiving penicillin she complained of dysuria and the urinalysis revealed 40 leukocytes in each microscopic field as viewed with the high power objective. Cultures of the vesical urine at this time revealed the presence of *Escherichia coli*. The urinary infection persisted until small doses of sulfathiazole were administered. The urinary infection subsided rapidly under sulfathiazole treatment, but a definite drug fever developed while she was being treated for the *Escherichia coli* infection. The fever was not associated with penicillin therapy and the temperature quickly returned to normal as soon as the administration of sulfathiazole was discontinued.

This is an excellent example of selective antibacterial activity of penicillin. It is obvious that penicillin was present in the urine in adequate amounts, but since penicillin is ineffective against *Escherichia coli*, the development of *Escherichia coli* bacilluria is quite understandable. No toxic manifestations whatever were associated with the administration of penicillin.

## COMMENT

These two cases of staphylococcic septicemia are somewhat similar. In one case, the septicemia resulted from a rather severe or extensive localized staphylococcic cellulitis of the face. In the other case, the septicemia was secondary to a very extensive cellulitis of the left arm. Both patients were obviously not responding to sulfonamide therapy. Both patients were over fifty years of age and, as previously pointed out, staphylococcic sepsis in this age group carries a high mortality. In both instances, the staphylococcic septicemia was complicated by rather extensive pneumonia. It must be assumed that the pneumonia was probably staphylococcic in origin. The presence of pneumonia complicating septicemia is a finding of grave prognostic significance. Both patients were treated with penicillin, which was administered by the intravenous drip technic. Thirty-two thousand Oxford units per day was administered in both instances. Both patients were treated early in our experience with penicillin therapy. We believe at the present time that 40,000 to 60,000 Oxford units per twenty-four hours is the most satisfactory dose, however, we have obtained satisfactory results in other cases by using only 32,000 Oxford units in twenty-four hours when the drug is given by the intravenous drip method.

It is of considerable interest that the patient in Case II had evidence of an infection of the urinary tract at the time of her admission to the hospital. She was treated at first with sulfathiazole because of the staphylococcic sepsis. No urinary symptoms were present while sulfathiazole was being administered, however, the staphylococcic sepsis was not responding satisfactorily to this therapy. The administration of sulfathiazole was discontinued and the staphylococcic sepsis was treated satisfactorily with penicillin. While she was receiving penicillin, she evidently had an *Escherichia coli* infection of the urinary tract, as evidenced by positive cultures. When very small amounts of sulfathiazole again were administered for the *Escherichia coli* infection a drug fever developed. This unquestionably was due to an acquired sensitivity to the drug. It is probable that had it been necessary to treat her with sulfathiazole alone she also may have exhibited this toxic manifestation to the drug. Penicillin is very effective against most gram positive pathogenic bacteria but as illustrated in Case II it was ineffective against a gram-negative organism. A knowledge of the selective antibacterial activity of penicillin as well as of other chemotherapeutic agents is exceedingly important in the successful treatment of bacterial infections. It should be emphasized that localized collections of pus probably should be drained in conjunction with penicillin.

therapy Penicillin therapy, or chemotherapy in general, is no substitute for sound medical judgment

Although we have used the continuous intravenous drip method of administering penicillin for the most part, it must be stated that the *intermittent intramuscular method* is also satisfactory We resort to this form of administration when suitable veins are not available When intramuscular therapy is used the usual dose employed is between 80,000 and 160,000 Oxford units per day<sup>3</sup> Ten thousand or 20,000 Oxford units of penicillin are dissolved in 4 or 5 cc of physiologic salt solution and administered intramuscularly into the gluteal or deltoid muscles The gluteal muscles are more desirable This method requires eight injections per day, therefore, it places considerable extra demand on the medical personnel Local regions of induration and pain may occur at the site of intramuscular injection The only local complication which has been observed after the continuous intravenous treatment with penicillin is the development of venous irritation at the site of injection (so-called penicillin phlebitis) This is probably due to the impurities present in the penicillin now available and is not due to penicillin per se If a satisfactory preparation of penicillin is available, this reaction will not occur in more than 5 per cent of cases Moist or dry packs applied locally to the site of irritation will usually result in rapid subsidence of this complication

Early institution of adequate penicillin therapy in the treatment of staphylococcic sepsis promises to reduce greatly the morbidity and mortality of this rather serious disease We believe that early and adequate treatment of cellulitis involving the soft parts will prevent not only the development of septicemia but also the development of distant metastatic abscesses and probably osteomyelitis subsequent to infection of the soft tissue

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# SULFONAMIDE TREATMENT OF BACTERIEMIA AND ACUTE BACTERIAL MENINGITIS

ALEX E. BROWN

BACTERIEMIA and acute bacterial meningitis have always been serious diseases which have been attended by high mortality rates. Both diseases have much in common. Both represent dissemination of bacteria in the body, usually from a primary focus. Meningitis represents in many instances but a further severe complicating phase of bacteriemia. At present, the treatment with the sulfonamides extends along parallel lines for both conditions.

It is of interest that only one of these diseases, namely meningococcic meningitis, while constantly present in sporadic form, has a tendency to occur during times of war in epidemics which have involved both civilian and military populations. It would seem possible that other types of these infections, particularly those arising from the upper part of the respiratory tract, might have a tendency to occur more frequently in sporadic form under similar prevailing conditions. In the first World War, 5,839 cases of meningococcic meningitis were observed among the troops of the United States Army.<sup>11</sup> The mortality rate in these cases was 39 per cent, which was lower than the prevailing mortality rate for this disease at that time. In 1940, 12,500 cases of cerebrospinal meningitis were reported to the Ministry of Health in England.<sup>12</sup> Awe, Barbione and DeLamater,<sup>1</sup> Daniels, Solomon and Jaquette,<sup>3</sup> and Hill and Lever<sup>9</sup> reported a total of 236 cases of meningococcic meningitis that were observed among the armed forces of the United States in the present World War. All of these cases were observed prior to April 18, 1943. Death occurred in five, or 2 per cent, of the 236 cases.

## ETIOLOGY

In 1938, E. C. Rosenow, Jr., and I<sup>10</sup> reported a study of a group of cases of bacteriemia that were observed at the Mayo Clinic in the years 1934 to 1936 inclusive. In 1941, Herrell and I<sup>7</sup> reported a study of a comparable group of cases that were observed during the years 1937 to 1939. The two reports comprised a study of 469 cases of bacteriemia. A positive blood culture was obtained in all of the cases. Such diseases as typhoid and paratyphoid fever and brucellosis were not included in either of these reports.

In the entire group of 469 cases of bacteriemia, blood cultures dis-

closed the following bacteria: green-producing streptococci, chiefly *Streptococcus salivarius* and *Streptococcus mitior*, in 167 cases,\* hemolytic streptococci in 107 cases, *Staphylococcus aureus* in seventy-three cases, *Diplococcus pneumoniae* in forty-three cases, *Escherichia coli* in thirty-five cases, *Bacteroides* in fourteen cases, small, gram-negative bacilli in ten cases, *Neisseria intracellularis* (meningococcus) in seven cases, *Areobacter aerogenes* in six cases, *Klebsiella pneumoniae* in two cases, and *Staphylococcus albus*, *Proteus ammoniae*, *Haemophilus influenzae*, *Pseudomonas* and *Streptobacillus moniliformis* in one case each

With few exceptions, the organisms which most frequently cause bacteriemia also are the most common causes of acute bacterial meningitis. The most common causes of the latter disease are *Neisseria intracellularis* (meningococcus), *Diplococcus pneumoniae*, hemolytic streptococci, *Haemophilus influenzae* and staphylococci. Although *Mycobacterium tuberculosis* is a common cause of meningitis, it is not affected by the sulfonamide drugs.

Of the various types of bacteriemia and meningitis that have been mentioned, that which is due to the *Neisseria intracellularis* (meningococcus) is the only one that has a tendency to occur in epidemics. Although the early prevailing opinion was that this type of meningitis resulted from direct invasion of the meninges through the cribriform plate of the ethmoid bone, recent observations tend to confirm the opinion of Herrick<sup>8</sup> that the infection of the meninges is the result of bacteriemia which in turn is the result of nasopharyngeal infection. The role of carriers in the spread of meningitis is not known definitely. In some instances the percentage of carriers has been found to be higher in localities in which an epidemic of meningitis does not exist than it has in localities in which such an epidemic exists. When an epidemic of cerebrospinal meningitis is present in a military area, as many as 80 per cent of the healthy troops may be carriers of *Neisseria intracellularis*.<sup>2</sup> When an epidemic is not present, the percentage of carriers may range from 2 to 10.<sup>4</sup>

In cases in which bacteriemia or meningitis is caused by hemolytic streptococci, the primary sources of infection most frequently will be found in the paranasal sinuses, in the middle ear or mastoid cells, in the skin or in the genito-urinary tract. Less common sites are the bones and lungs. When this type of bacteriemia or meningitis exists in the absence of local infection, the presence of endocarditis or of thrombophlebitis, especially of the pelvis or skull, should be suspected.

In pneumococcic bacteriemia or meningitis, the primary source of

\* Subacute bacterial endocarditis was present in 151 of the 167 cases.

infection usually will be found in the lungs, paranasal sinuses, middle ear or mastoid cells and at times in bone, particularly in cases in which the patients are children.

Staphylococcic bacteriemia or meningitis most frequently occurs as a result of primary infection in the skin, such as a carbuncle, or as a result of infection of bone, such as osteomyelitis. It may also arise from the respiratory or genito-urinary tract. The disease may develop a considerable time, even one or two months, after healing of the primary focus.

The normal habitat of *Escherichia coli* is the gastro-intestinal tract and bacteriemia due to this organism most frequently results from operative procedures on this or the genito-urinary tract.

Meningitis or bacteriemia produced by *Haemophilus influenzae* is chiefly a disease of infants and children. In about 75 per cent of cases of influenzal meningitis, the patients are two months to three years of age. In these cases, the meningitis probably occurs as a primary infection associated with a respiratory infection, and usually is associated with bacteriemia. In cases in which the patients are more than three years of age, influenzal meningitis usually is secondary to a focus of infection in the mastoid cells, middle ear or paranasal sinuses, or it is the result of injury of the head.

#### DIAGNOSIS OF BACTERIEMIA AND MENINGITIS

Although space does not permit a detailed consideration of the diagnosis of bacteriemia and acute meningitis, it is important to emphasize that the general symptoms and signs of infection exist in each case. In bacteriemia the clinical picture is usually one of sepsis, which is frequently associated with chills and fever.

The existence of signs and symptoms of infection with or without the presence of a detectable focus of infection should bring to mind the question of bacteriemia. This is particularly true when the degree of sepsis appears out of proportion to any discernible causative factor. In acute bacterial meningitis this same foregoing picture of bacteriemia is frequently present. This is particularly important in epidemics of meningococcic meningitis, as Daniels, Solomon and Jaquette<sup>3</sup> recently have shown that it frequently is possible to treat patients while they are in a phase of meningococcemia rather than in a stage of meningitis.

Hemorrhagic conditions of the skin and mucous membranes occur in a large proportion of cases of meningococcic meningitis and also occur at times in cases of influenzal meningitis. Headache with or without nausea and vomiting has occurred in a large percentage of truly reported cases of meningococcic meningitis, other similar

more characteristic symptoms are stupor, convulsions and coma. The last symptom has proved to be of grave prognostic significance in recent epidemics of meningococcic meningitis.

Either increased intracranial pressure or meningeal irritation may be evidenced by localizing signs. These signs, in the case of increased intracranial pressure, may be manifested by engorgement of the veins of the ocular fundi or by choked disk. Meningeal irritation may give rise to spasm of the muscles of the neck or back or of the hamstring group of muscles, with resultant stiffness of the neck or back, or a positive Kernig sign. The presence of symptoms or signs of this type constitutes an indication for detailed examination of the spinal fluid, including a cell count and chemical analysis, but exact diagnosis and proper treatment are dependent on positive identification of organisms by smear or culture.

#### TREATMENT

**Sulfonamide Drugs**—Five sulfonamide drugs are available for the treatment of bacteriemia and acute bacterial meningitis. In the order of their introduction they are sulfanilamide, sulfapyridine, sulfathiazole, sulfadiazine and sulfamerazine. The last named compound is the monomethyl derivative of sulfadiazine, which recently has been released for use. Experimental work now is being carried out with the dimethyl derivative of sulfadiazine, which is known as sulfamethazine, but this compound is not available for general use at present.

*Pharmacologic Properties*—It is well to have some knowledge of the pharmacologic properties of all of these drugs because under certain circumstances it may be necessary to use any one of them. The accompanying table shows the solubility, absorption, excretion, acetylation, diffusion, toxicity and bacteriostatic effect of these drugs. With the exception of sulfanilamide, these drugs are poorly soluble, therefore, when one desires to administer sulfapyridine, sulfathiazole, sulfadiazine or sulfamerazine parenterally, it will be necessary to use the more soluble sodium salt of the respective drug. Sulfamerazine is about two and a half times as soluble as sulfadiazine.

All of these drugs are well absorbed when given orally, but sulfapyridine may be absorbed irregularly and sulfamerazine appears to be absorbed more rapidly and completely than are the others. This irregularity of absorption of sulfapyridine may exist not only among individuals but may occur from day to day in the same patient. It may result in failure to produce satisfactory concentrations of the drug in the body. This difficulty of absorption may be eliminated by administering the sodium salt of sulfapyridine parenterally.

All of the drugs are well excreted in the urine, but sulfathiazole at

times may be excreted so rapidly that it may be impossible to obtain a satisfactory concentration of the drug in the body. This may be true even when the drug is administered parenterally. Both sulfadiazine and sulfamerazine tend to be excreted more slowly than the other drugs that have been mentioned. Sulfamerazine is excreted more slowly than sulfadiazine is. These two drugs tend to accumulate in higher concentrations in the body than do the other drugs.

Acetylation occurs with the administration of any sulfonamide and is detrimental because the acetyl derivatives of the sulfonamides are therapeutically inactive and in general are relatively insoluble. Because of their insolubility, they are eliminated with difficulty by the kidneys. Sulfadiazine and sulfamerazine possess an advantage over the other

PHARMACOLOGIC PROPERTIES OF SULFONAMIDE DRUGS

Influencing Factors	Sulfanilamide	Sulfapyridine	Sulfathiazole	Sulfadiazine	Sulfamerazine
Solubility in water at room temperature	1 per cent	0.03 per cent	0.1 per cent	0.01 per cent	0.025 per cent
Absorption	Good	Fair (irregular)	Good	Good	Good (complete)
Excretion	Good	Good	Good (?) (rapid)	Good (slow)	Good (slow)
Acetylation	Slight (10-15 per cent)	Great (15-75 per cent)	Slight (10-30 per cent)	Slight (10-15 per cent)	Slight (5-10 per cent)
Concentration in spinal fluid†	80-90 per cent	60-80 per cent	30 per cent	60-80 per cent	Not definitely known
Toxicity	Moderate	Moderate +	Moderate ++	Mild	Mild
Bacteriostatic effect	Hemolytic streptococci and meningococci	Hemolytic streptococci, parvumococci, staphylococci and meningococci			

Compressed insoluble.

† Compared with concentration in blood.

drugs, except sulfanilamide, in that their acetyl derivatives are more soluble in urine than are the acetyl derivatives of the other drugs. It may be noted that only from 10 to 15 per cent of sulfanilamide and sulfadiazine and from 5 to 10 per cent of sulfamerazine forms an acetyl derivative, but that from 10 to 30 per cent of sulfathiazole and from 15 to 70 per cent of sulfapyridine undergo this change.

Diffusion of drug into the cerebrospinal fluid is important in meningitis and it may be noted in the table that with sulfathiazole this diffusion amounts to only about 30 per cent of the concentration of the drug in the blood, whereas with the other compounds it is two or two and a half times this figure. In spite of this poor diffusion, sulfathiazole, as is known, is effective in the treatment of meningitis.



From the standpoint of bacteriostatic action, sulfanilamide possesses a definite disadvantage because it is effective chiefly against only hemolytic streptococci and *Neisseria intracellularis* (meningococcus). Therefore, it should not be used when the causative organism is unknown. All of the other sulfonamides are effective against these and to some extent against other organisms which have been mentioned as common causative agents of bacteriemia and meningitis. Sulfathiazole seems most effective against staphylococci and sulfadiazine against *Haemophilus influenzae*. The action of all of the sulfonamides on staphylococci is considerably inferior to their action on hemolytic streptococci. When penicillin is available, it is much more effective against this infection. With all of the foregoing in mind, accumulated experience would indicate that sulfadiazine appears to possess advantages which make it the sulfonamide of choice in the treatment of bacteriemia and meningitis at this time. Sulfamerazine, however, because of its greater solubility and tendency to accumulate in higher concentrations in the body with less frequent administration seems to possess advantages which in the light of further experience may well cause it to supplant sulfadiazine.

*Fundamental Principles of Treatment with the Sulfonamides*—In the treatment of bacteriemia and meningitis with the sulfonamides, there are certain fundamentals which are important. In the first place, in cases in which the infection is severe, the best results will be obtained if accurate control is kept of the concentration of the sulfonamide in the blood. If facilities for the determination of this concentration are lacking, treatment must be dependent on the clinical response on the one hand and on toxic symptoms on the other, but this is an unsatisfactory and hazardous method owing to the variations in absorption, excretion and acetylation of these drugs.

It is necessary to bear in mind that the action of the sulfonamides appears to depend on only two factors: (1) their ability to reduce the multiplication of organisms and (2) their ability to weaken organisms so that they can be overcome by the normal defense mechanisms of the body. Thus the early administration of the sulfonamides is indicated if the treatment of infection is to be simplified.

It is supposed that the action of the sulfonamides is inhibited by peptone, which is derived from the protein of broken down tissue, and by para-aminobenzoic acid. Both of these substances seem necessary for bacterial metabolism, and when they are present in excess, bacteria take them up in preference to the sulfonamides. It therefore is essential to treat severe infection before it becomes extensive and causes destruction of tissue. Experience has shown that the best results are

obtained in cases of bacteriemia or meningitis when the desired concentration of the drug in the blood is obtained as soon as possible and maintained until recovery occurs. Undoubtedly the period of illness has been prolonged and many lives have even been lost because of delay for twenty-four to forty-eight hours in starting treatment while awaiting some laboratory report, such as the result of a culture. Treatment always should be started when the presence of bacteriemia or meningitis is suspected, if no contraindications exist. A culture of the blood or spinal fluid should be made at the same time but further details of the diagnostic picture can be established later. In cases in which one of the sulfonamide drugs is being administered, the addition of 5 mg of para aminobenzoic acid to each 100 cc of culture medium frequently will facilitate bacterial growth.

Doses sufficient to maintain the desired concentration of the drug in the blood should be continued for about four days after the temperature and pulse rate have returned to normal. Reduced doses of the drug then should be administered until the temperature and pulse have remained normal for two weeks. In cases of staphylococcal or pneumococcal bacteriemia or meningitis, it is advisable to continue the administration of one of the sulfonamides for three weeks after the temperature has returned to normal, in order to reduce the possibility of a recurrence of the infection.

**Dosage**—Experience at the Clinic has indicated that moderately high concentrations of drug in the blood are desirable. We thus try to obtain concentrations of 16 mg of sulfanilamide, sulfapyridine and sulfathiazole per 100 cc. of blood. We have not had sufficient experience with sulfamerazine to be certain of a desirable concentration but a concentration of this drug also would seem advisable. In the case of sulfathiazole, a concentration of 10 to 14 mg per 100 cc seems best. Such concentrations usually are obtained most rapidly in adults by administering the sodium salt of the drug intravenously in a total dose of between 5 and 10 g.

administration of the drug is repeated every four hours. A second intravenous dose of the sodium salt of the drug usually is given at the end of seven hours. The concentration of the drug in the blood is checked two or three times daily for several days. We supplemented oral administration of the drug by parenteral administration of the sodium salt as necessary to maintain the desired concentration of the drug.

In using sulfadiazine orally the drug usually may be administered at intervals of six hours and sulfamerazine may be given at intervals of eight hours instead of four. The sodium salts of both these drugs usually can be administered parenterally at intervals of twelve hours instead of eight. The concentration of sulfamerazine also can usually be maintained with smaller doses than necessary with the other sulfonamides. Recently, some authors have mentioned the successful use of sulfadiazine in concentrations as low as 8 mg per 100 cc of blood in order to lessen the occurrence of renal complications in cases of meningococcic meningitis, but I have had no experience with these concentrations in this condition and my experience in the other types of meningitis has indicated the necessity for higher concentrations. By administering the drugs intravenously initially, the need for intrathecal administration appears to be obviated and the possible dangers of this method of administration also may be eliminated.

*Toxicity of and Toxic Reactions to the Sulfonamide Drugs*—All of the sulfonamide drugs have a tendency to produce toxic effects. As all of these drugs are closely related chemically, their toxic effects are similar. These toxic manifestations are generally known but there are a number of points which should be emphasized.

Although sulfadiazine may produce renal complications, it is less toxic than sulfathiazole, sulfapyridine or sulfanilamide. To date, sulfamerazine appears to be about as toxic as sulfadiazine. Sulfathiazole is the most toxic of these sulfonamides. Although sulfapyridine and sulfanilamide occupy an intermediate position in regard to the production of toxic effects, sulfapyridine is probably more toxic than sulfanilamide. The longer the sulfonamide drugs are administered, the greater appears to be the likelihood that they will produce toxic manifestations. Bacteriemia and meningitis constitute a greater hazard from this standpoint than do less severe infections which require treatment for a shorter time.

It should be emphasized that, with the exception of *leukopenia* and *granulocytopenia*, all of the toxic manifestations of the sulfonamides can be detected by clinical observation alone. Sulfapyridine and sulfanilamide are more likely to cause leukopenia and granulocytopenia.

than are the other sulfonamides. It is important to remember that in cases in which granulocytopenia occurs as a toxic manifestation of a sulfonamide it rarely occurs before the drug has been administered for two weeks. Sulfanilamide and sulfapyridine are more likely to cause *acute anemia* than are any of the other sulfonamides. This toxic manifestation usually occurs in the first week of treatment. Granulocytopenia and acute anemia, as well as *jaundice*, which also may occur as a toxic manifestation, are indications for discontinuing the administration of these drugs.

*Drug fever* and *drug rash*, which may or may not be associated, occur more frequently as a result of administration of sulfathiazole than they do as a result of administration of the other sulfonamides. They usually occur after the drug has been administered for nine to twelve days but may occur before or after this period. Both of these manifestations usually represent a sensitivity reaction which may be related to previous administration of the drug. Drug fever often is high and may be associated with chills and fever. It always should be suspected when improvement, produced by a sulfonamide, is followed by recurrence of fever while the drug still is being administered. It should be emphasized, however, that fever that occurs during convalescence should be suspected of being due to relapse rather than to a sensitivity reaction until proved otherwise. Drug fever or drug rash is ordinarily an indication for discontinuing the administration of the sulfonamide drugs. In cases of bacteriemia and meningitis, the administration of these drugs usually is essential rather than optional, therefore, when a drug rash or fever occurs, the administration of the offending sulfonamide should be discontinued and another sulfonamide should be administered under close observation if possible. At the Clinic, we frequently have seen a drug rash or drug fever disappear when the administration of sulfanilamide or sulfathiazole was discontinued and another sulfonamide drug such as sulfadiazine was administered.

*Renal complications* constitute a real hazard in the administration of all the sulfonamide drugs except sulfanilamide. These complications occur more frequently in conjunction with the administration of sulfathiazole and sulfapyridine than they do in conjunction with the administration of sulfadiazine and sulfamerazine although they may occur with administration of the latter drugs. These complications include anuria, renal pain and severe hematuria. Crystalluria, when it occurs alone, is not a renal complication of the administration of these drugs, in fact, it is a frequent occurrence. Renal insufficiency may result from toxic injury of the kidney or from urinary obstruction that is caused by crystals of sulfonamide. As all of the sulfonamide

drugs are eliminated almost entirely in the urine, maintenance of a fluid intake of 3,000 cc or more and of a urinary output of 1,400 cc or more daily will do much to prevent renal complications. By following this procedure, oliguria frequently will become evident before the onset of anuria and the margin of safety will be greater than it would be if a low intake of fluid and a low excretion of urine were maintained. If renal complications do occur, they usually can be treated successfully by promptly discontinuing the administration of the offending sulfonamide, by increasing the administration of fluids within reason, by administering aminophylline and a hypertonic solution of dextrose and finally, at times, by ureteral catheterization.

**Adjuvant Alkali Therapy**—The use of an alkali as an adjuvant, as suggested by Gilligan, Garb, Wheeler and Plummer,<sup>6</sup> tends to lessen the incidence of renal complications in cases in which sulfadiazine or sulfamerazine is being administered. These investigators have demonstrated that sulfadiazine is twenty times more soluble and that acetylsulfadiazine is thirty times more soluble at a hydrogen ion concentration of 7.5 than they are at a concentration of 5.0. They also have demonstrated that sulfadiazine is seven times more soluble and that acetylsulfadiazine is thirteen times more soluble at neutrality, that is at a hydrogen ion concentration of 7.0, than they are at a concentration of 5.0. These findings are extremely important. When one considers that sulfadiazine itself has a tendency to acidify urine and that in most cases in which sulfadiazine is administered the hydrogen ion concentration of the urine is 5.0 to 6.0, there would seem to be ample reason for employing adjuvant alkali therapy in conjunction with the administration of this drug. These investigators suggested the administration of an initial dose of 6 gm of sodium bicarbonate and the subsequent administration of 2.6 gm of this drug every four hours until six doses have been administered. The solubility of sulfamerazine would indicate that adjuvant alkali therapy should be of considerable value when used in conjunction with this drug. This type of therapy probably would be of some value when used in conjunction with sulfathiazole. The solubility of sulfapyridine precludes any favorable effect of adjuvant alkali therapy when used with this drug. When using this type of therapy, it is possible to check the pH of the urine roughly by using litmus or nitrazine paper, which turns blue in urine that is neutral or alkaline.

**Supplementary Treatment**—As adjuncts to the successful use of the sulfonamide drugs in cases of bacteremia or meningitis, the following procedures will be found of value. When there is any focus of infection that can be eradicated by *operation*, it is advisable to operate if

recovery is to be expected. In cases of prolonged infection in which debility is present, *transfusion* of 250 cc. of whole blood is advisable at intervals of two or three days, both for the relief of anemia, if present, and for the relief of the toxemia. Patients who become debilitated may be benefited by the use of *vitamins*.

In cases of severe bacteriemia caused by hemolytic streptococci, administration of convalescent scarlet fever serum may be of some benefit in combating the toxemia. The same thing may be said for the use of staphylococcic antitoxin in cases of staphylococcic bacteriemia.

The question of the use of *specific serum* as adjuncts to sulfonamide therapy is one about which there is bound to be some divergence of opinion until a large number of cases have been studied. Recent experience by physicians who have treated large numbers of patients indicates, however, that in the treatment of meningococcic meningitis the use of specific serum adds little or nothing to the effect of sulfonamides. The problem, however, is different in pneumococcic meningitis because of the high mortality rate which has existed with all methods of treatment. In this type of meningitis, type specific serum seems to be indicated if it is available. Although we have had but little experience with influenzal meningitis at the Clinic, the same situation would seem to prevail here as with pneumococcic infections.

It has been our experience that when sulfonamides are used in the treatment of meningitis, *spinal puncture* seems necessary only as a diagnostic measure or for the relief of symptoms such as headache, which may result from increased intracranial pressure.

## RESULTS

In cases of bacteriemia or subacute bacterial meningitis the results of sulfonamide therapy have been particularly impressive. The best evidence of the value of the sulfonamide drugs in the treatment of these diseases can be obtained by comparing the results obtained with and without the use of these drugs.

**Bacteriemia.**—Prior to the use of sulfonamides the mortality rate in cases of hemolytic streptococcic or staphylococcic bacteriemia was 70 to 87 per cent but with use of sulfonamides it decreased to 20 to 35 per cent for the former group and to 35 to 50 per cent for the latter group. The mortality rate in cases of *Escherichia coli* bacteriemia showed a marked decrease to about 22 per cent with use of sulfonamides from a previous 43 per cent. Our own treatment of bacteriemia caused by *Diplococcus pneumoniae* in the early years of sulfonamides showed no improvement in results from previous years when the mortality rate was about 70 per cent without use of sulfonamides.

However, with the introduction of sulfonamides more specific for the pneumococcus than sulfanilamide and with the combined use of type specific serum the results have been definitely improved. It is of interest also that at the Clinic we have seen one patient recover from severe bacteriemia caused by bacteroides after the use of sulfapyridine. Previously this condition had carried a 100 per cent mortality rate in our own experience.

It is well to point out that adherence to cardinal principles of treatment will produce the most successful results. Naturally the prognosis for younger patients is best but the prognosis for older patients who have bacteriemia has been tremendously improved with the use of sulfonamides. Certain complications as the development of a focus directly connected with the circulating blood as with endocarditis or thrombophlebitis, continue to form insurmountable barriers to successful treatment, but early and adequate treatment should lessen the occurrence of these complications.

**Meningitis**—A similar improvement in mortality rates has attended the use of sulfonamides in meningitis, although it must be remembered that this condition is usually more severe than bacteriemia and that it frequently represents the imposition of meningitis on bacteriemia. General statistics are cited because they are of more interest than smaller series of cases from the Clinic. They indicate that the mortality rate in meningococcic meningitis decreased from between 90 and 40 per cent to between 30 and 17 per cent with use of serum and that it has decreased still further with use of sulfonamides to a remarkable figure which is somewhere between 12 and 0 per cent. In pneumococcic meningitis the previously existing mortality rate of from 99 to 100 per cent has been decreased to between 80 and 35 per cent with the use of certain sulfonamides. Hemolytic streptococcic meningitis was attended by a mortality rate of about 97 per cent before sulfonamides came into use, but since their employment this figure has decreased to from 40 to 20 per cent in different groups throughout the country. In influenzal meningitis use of serum and sulfonamides has caused a decrease in mortality rates to 49 per cent from a previous 98 to 100 per cent. In staphylococcic meningitis, the results of course are not as good as those obtained in the foregoing types of meningitis, but recoveries have been noted from the use of sulfonamides in this condition which previously was almost 100 per cent fatal.

#### COMMENT

As time has gone on the value of sulfonamides in the treatment of common forms of bacteriemia and meningitis has been increasingly

demonstrated. It has also shown that the prognosis in these conditions is largely conditioned on the promptness with which treatment is started as well as on the maintenance of adequate dosage with sulfonamides throughout the course of illness and for a long enough period after the disease is under control to prevent recurrences. Serious complications from the drug may be markedly decreased by careful observation of the patient under treatment and if complications do occur they frequently will subside satisfactorily if they are promptly and appropriately treated.

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# THE USE OF THE SULFONAMIDES IN THE TREATMENT OF DISEASES OF INFANCY AND CHILDHOOD

GEORGE B LOGAN

THE practice of pediatrics is general practice confined to an age group. The indications for and the use of the sulfonamide drugs in the treatment of disease of infancy and childhood are much the same as those in adult practice. However, some aspects of administration and dosage and the advisability of their use in the treatment of certain diseases require particular comment.

## MODES OF ADMINISTRATION

The *oral route* for the administration of sulfonamides is the one most generally employed. In the case of older children, objections to swallowing pills frequently are negligible. For younger children and infants, the pills either must be crushed or the medicine prescribed in the form of a powder. This can be given mixed with honey, syrup or jelly. Sulfadiazine may be prescribed in syrup such as syrup of cherry (NF) in the proportions of 5 gm of powder to each 60 cc of syrup.<sup>7</sup> Such a mixture contains 5 grains (0.3 gm) of sulfadiazine in each teaspoonful (4 cc). It must be shaken well before each dose is given.

Sulfathiazole gum is now available and may be a useful means of administering the drug. In the case of young children who are able to chew gum, a satisfactory concentration of the drug in the blood may be achieved with the use of this material, but in the case of older children, more than a local effect probably cannot be secured.

Poncher<sup>7</sup> has described sulfadiazine and sulfapyrazine lozenges composed of the drug, acacia and sugar. They are not available commercially. Recently sulfathiazole, sulfadiazine and sulfamerazine have been put on the market in candy form. Each tablet contains 5 grains (0.3 gm) of the drug.

Vomiting, coma, inability to swallow or downright refusal of the child to take the medicine make other means of administration necessary. Park<sup>6</sup> has suggested *rectal administration* of the sulfonamide drugs in suppositories made of cocoa butter. Suppositories that contain 0.5 or 1 gm of the drug have been recommended. The patient is given a preliminary cleansing enema of warm water. Then the suppository is inserted, after which the buttocks are held together for twenty to thirty minutes by hand or by adhesive plaster. The dose,

when thus administered, should be twice as large as that administered orally

*Parenteral administration* of the sulfonamides is often necessary For this purpose the sodium salts of the various sulfonamide drugs are used The exception to this is sulfanilamide, which is used as an 0.8 per cent solution in distilled water or physiologic salt solution

The solutions in which the sodium salts of the sulfonamides may be used are important. Distilled water is frequently used, and, with this, solutions of 0.5, 1 and 5 per cent are most commonly employed For some time, physiologic salt solution was the only other solvent advised However, a sixth molar solution of sodium lactate, a 5 per cent solution of dextrose in distilled water or a 5 per cent solution of dextrose in physiologic salt solution have been found to be satisfactory solvents In the Section on Pediatrics we have used all but the lactate solution and have encountered no untoward reactions The solvents are best prepared first and the sulfonamide added later

A satisfactory method for the preparation of a 0.5 per cent solution is to add 100 cc. of freshly prepared 5 per cent solution of the sodium salt in distilled water to 900 cc. of one of the above mentioned vehicles Each 100 cc. of the resultant solution will represent 0.5 gm. of the drug One should not add sulfonamides to blood which is to be given by transfusion or to solutions containing blood or serum which are intended for intravenous or intramuscular administration

The *intravenous route* is usually employed when a high concentration of the drug in the blood is desired promptly Should a continuous intravenous infusion already be running, a 5 per cent solution of the sulfonamide may be put into the container that holds the solution or it may be introduced at intervals through the rubber tubing by means of a hypodermic needle and syringe However, frequent intravenous administration is neither necessary nor practical in a case in which the patient is a child whose available veins are limited

The *intramuscular route* has been used but is not recommended If continuous parenteral administration is necessary, we prefer to use the *subcutaneous route* Solutions of varying strengths have been employed Those of 0.5 to 1 per cent have been most widely advocated and serve a double purpose in cases in which fluids must be administered parenterally to combat dehydration The daily dose may be divided into two or three parts, to be given at intervals of eight to twelve hours or it may be given as a continuous drip infusion We have found that 0.5 and 1 per cent solutions of sodium sulfapyridine, sodium sulfathiazole, sodium sulfadiazine and sodium sulfamerazine can be given subcutaneously without causing irritation.

At times one may desire to give stronger solutions subcutaneously. Shortly after the appearance of a report by Jorgensen and Greeley<sup>5</sup> we began to use a 5 per cent solution of sodium sulfadiazine in distilled water. We have administered it to infants and children of all ages and have observed no untoward reactions. Theoretically its hydrogen ion concentration of 9.9 should contraindicate its use, nevertheless, it may be employed with safety.

We have not as yet given a 5 per cent solution of the sodium salt of sulfathiazole subcutaneously but we have employed a 5 per cent solution of the sodium salt of sulfamerazine subcutaneously with no untoward reaction.

#### DOSAGE

The sulfonamides should be given in full therapeutic doses. Common mistakes are to give too little and to stop the administration too soon. The usual rule for oral administration of sulfanilamide is to give an amount equal to  $\frac{3}{4}$  grain (0.05 gm) of the drug per pound (0.5 kg) of body weight, each twenty-four hours. This amount is divided into six doses, one of which is given every four hours. Sulfapyridine, sulfathiazole and sulfadiazine are given in amounts of 1 grain (0.065 gm) per pound every twenty-four hours, divided into six doses. Because of its slow rate of excretion, sulfadiazine may be given at intervals of six hours. The dose of sulfamerazine is the same as that of sulfadiazine. Recently it has been suggested that the maintenance dose of sulfamerazine is only half that of sulfadiazine and that it need be given only every eight hours.

Sulfapyrazine,<sup>1</sup> a new drug, seems to hold some promise. The dose recommended is  $1\frac{1}{2}$  grains (0.1 gm) per pound (0.5 kg) of body weight each twenty-four hours, given in four doses.

When children attain the age of eleven or twelve years and their weight exceeds 90 pounds (40.8 kg), the dose need no longer be based on weight and the adult tables of dosage may be employed.

Administration of the sulfonamides is best begun by giving half the twenty-four hour dose as the initial dose. If this seems too much at one time, a fourth to a third of the amount may be given, followed in two hours by another fourth to a third of the daily dose and thereafter by the doses regularly administered every four to six hours.

For the most part, oral administration will maintain a satisfactory concentration of the drugs in the blood. A determination of this concentration should be carried out twenty-four hours after the administration of the drug has been started. Should facilities for this not be available, the clinical course of the patient will have to determine the adequacy of the dose. If satisfactory progress is not made in twenty-

four to forty-eight hours, hospitalization should be considered. In the treatment of the diseases for which the various drugs are indicated, the following concentrations in the blood are generally adequate:

Sulfanilamide	8 to 10 mg per 100 cc.
Sulfapyridine	10 to 12 mg per 100 cc.
Sulfathiazole	4 to 6 mg per 100 cc.
Sulfadiazine	10 to 12 mg per 100 cc.
Sulfamerazine	10 to 15 mg per 100 cc.

In the treatment of severe infections, the dose may have to be increased and the concentration of the drug in the blood maintained at 15 to 30 mg per 100 cc. in the case of sulfapyridine and sulfadiazine and at 10 to 12 mg per 100 cc. in the case of sulfathiazole. It is sometimes impossible to raise the concentration of the drug in the blood to satisfactory levels by oral administration and this method therefore may have to be supplemented or replaced by the parenteral method. When the sulfonamides are administered subcutaneously, a total daily dose of  $\frac{3}{4}$  grain (0.05 gm.) per pound (0.5 kg.) of body weight will often produce a satisfactory concentration, although 1 grain (0.065 gm.) or even more per pound of body weight may be necessary.

In a case of pneumococcal meningitis in which the patient was a child aged three years, we obtained a concentration of 36 mg. of sulfapyridine per 100 cc. of blood by administering the drug subcutaneously. The child recovered. Higher concentrations have been reported by other authors.

The sulfonamide compounds are apparently absorbed a little irregularly whether given orally or subcutaneously. This means that a dose which is adequate for one child may be either insufficient or more than enough for another child of similar age and weight.

In the treatment of severe infections the initial dose of  $\frac{1}{3}$  to  $\frac{1}{2}$  grain (0.02 to 0.032 gm.) per pound (0.5 kg.) of body weight may best be given intravenously. This is to be followed by the maintenance dose of the drug which is administered at once either orally or subcutaneously.

The concomitant administration of sodium bicarbonate is advisable when sulfapyridine, sulfathiazole or sulfadiazine is being employed. Enough should be given so that the reaction of the urine of the patient is neutral or alkaline. If this procedure is carried out the incidence of renal complications due to the precipitation of the sulfonamides in the tubules is reduced. However it does not abolish such complications. The oral dose of sodium bicarbonate is generally at least that of the sulfonamide being employed, often it is twice or more the sulfonamide.

Children treated with the sulfonamides may

reactions as do adults. We have encountered leukopenia, hematuria, renal suppression, erythema nodosum, scarlatiniform skin eruption and hemorrhagic bullae of the skin, as well as nausea and vomiting. Hemolytic anemia has been reported by others. All of the sulfonamides seem capable of producing these symptoms despite initial reports as to their lack of toxicity. Sulfanilamide, however, has not been known to produce harmful effects on the kidneys.

When these drugs are employed, erythrocyte and leukocyte counts should be made daily or at least every second day. The daily intake of fluids and the output of urine should be measured. In infants it may be possible to chart only the number of daily voidings.

The use of the sulfonamide drugs in the treatment of a dehydrated child without preliminary or concomitant hydrating therapy is dangerous. For infants care should be observed to see that the local use of a sulfonamide does not lead to undesired absorption of the drug.

#### DISEASES

Of the various disease conditions in which the sulfonamides are indicated, several deserve special mention because of their importance in the practice of pediatrics. Otherwise the consideration of the treatment in the other sections of this symposium are adequate for physicians interested in the care of children.

**Gonorrheal Ophthalmia**—The treatment of this disease was formerly a tedious, time-consuming procedure. We fortunately have not observed any cases of it recently. The oral administration of sulfonamides in conjunction with local irrigations with various preparations of silver or mercury has been found to be an improvement over older methods of treatment. In a recent article, Blumberg and Gleich<sup>2</sup> stated that they obtained excellent results with the oral administration of sulfathiazole alone. This was given as an emulsion in acacia. The initial dose was 3 grains (0.2 gm). This was followed by the administration of 1 gram (0.065 gm) every four hours until symptoms disappeared and smears from the conjunctival sac showed no gram-negative diplococci, which usually required from three to four days. The only local treatment employed in these cases was simple cleansing of the eyes.

**Meningitis**—Large doses of the sulfonamides are usually necessary in the treatment of cases of meningitis, particularly in those cases in which the infection is due to the *Haemophilus influenzae*, *Diplococcus pneumoniae*, or streptococci. Sulfadiazine is the drug of choice. Sulfathiazole also has produced good results despite its apparent inability to penetrate the barrier between the blood and spinal fluid. Sulfapyridine will often be found to be the most effective sulfonamide in cases

of pneumonococcic meningitis. It is wise to continue therapy for seven to ten days after the temperature has fallen to normal and after the culture of the spinal fluid has become negative. During this period the dose may be reduced by a third to a half.

**Acute Otitis Media**—Sulfadiazine, sulfathiazole or sulfamerazine is usually employed for acute otitis media. A full dose should be given until the symptoms and signs have subsided and the temperature has remained normal for at least seventy-two hours. The dose may then be cut in half. The reduced dose should be administered for several days after the patient appears to have recovered completely. Some physicians feel that this is a needlessly long time for administration of a sulfonamide drug but it has been our experience that recurrences of infection have taken place in some cases in which administration has been stopped too soon. It should be emphasized that in treating otitis media with sulfonamides inadequate therapy may actually result in harm by masking symptoms and thus allowing mastoiditis to develop without disclosing its presence by signs or symptoms.

**Acute Tonsillitis**.—The child who has tonsillitis usually does not require treatment with the sulfonamides. Should there, however, be any evidence of spread of infection to the middle ear or to the cervical lymph nodes, chemotherapy should be instituted.

**Acute Cervical Adenitis**—Some physicians believe that the sulfonamides have no place in the treatment of this condition. The use of sulfathiazole, sulfadiazine or sulfamerazine, however, often seems to shorten the course of the illness. Full doses are given until the temperature has been at or near normal for about forty-eight hours, half doses may then be given for seven to ten days. Other measures customarily used may be employed concomitantly.

**Acute Laryngotracheobronchitis**—Full doses of sulfadiazine, sulfathiazole or sulfamerazine should be given until the disease is under control. However, this part of the treatment is only supplementary to measures such as the use of steam, moist oxygen, tracheotomy and bronchoscopy.

**Pneumonia**—The prognosis of primary pneumonia in cases in which the patients are two to twelve years of age was good even in the years before the introduction of the sulfonamide drugs. However the use of these drugs has reduced the mortality rate still further. One should not neglect the usual symptomatic therapy.

The sulfonamide drug is given in full doses until the temperature has been normal for forty-eight to seventy-two hours. It is then halved for one day and if clinical improvement continues the use of the drug is then discontinued.

Sulfadiazine, sulfathiazole and sulfamerazine are the drugs of choice. If the recent reports on the good results produced by sulfapyrazine are substantiated, it too will be a valuable agent in the treatment of pneumonia.

Bronchopneumonia in infants has been much more effectively treated since the advent of the sulfonamides but, even when these drugs are given in large doses and their use is combined with all known supportive measures, the affected infant may not survive.

**Urinary Infections**—Sulfathiazole is the drug of choice for treatment of patients with infections of the urinary tract, except in those cases in which the infecting bacterium is *Streptococcus faecalis*. The dose is  $\frac{1}{2}$  grain (0.032 gm) per pound (0.5 kg) of body weight in twenty-four hours or no more than 45 grains (3 gm) as a total daily dose. None of the sulfonamides have been found to affect *Streptococcus faecalis*. Mandelic acid in some form must be used when this is the infecting organism.

**Dysentery**—Sulfathiazole, sulfaguanidine and succinylsulfathiazole have been used successfully in treatment of dysentery of various types. The stools should be cultured. The daily dose of sulfathiazole should be 1 to  $1\frac{1}{2}$  grains (0.065 to 0.1 gm) per pound (0.5 kg) of body weight (0.12 to 0.29 gm per kilogram). The daily dose of sulfaguanidine and succinylsulfathiazole is 2 to 4 grains (0.13 to 0.26 gm) per pound (0.5 kg) of body weight. The drugs are administered every four hours. In one epidemic of neonatal diarrhea,<sup>8</sup> succinylsulfathiazole (sulfasuxidine) was successfully used. No pathogenic organisms were found in the stools. The routine use of the sulfonamides in the non-dysenteric diarrheal diseases of infancy and childhood is not recommended.

**Communicable Diseases**—In the treatment of *scarlet fever*, the use of sulfanilamide or sulfadiazine is often worth while. Although they have no effect on the toxins produced by the bacteria, they may, by acting on the organisms, reduce the production of toxins. The incidence of direct complications such as otitis media and cervical adenitis seems to be reduced by adequate sulfonamide therapy.

*Measles* per se is not influenced by the use of the sulfonamides. Complications caused by streptococci and pneumococci respond to their use. Sulfadiazine is probably most effective, but sulfathiazole or sulfamerazine can be used with good effect.

The sulfonamides may be used in the treatment of *pertussis pneumonia*, although they exert no effect upon the *Haemophilus pertussis*.

Chickenpox and mumps, being virus diseases, cannot be expected to

be influenced by the use of sulfonamide drugs. Diphtheria also is uninfluenced, antitoxin is still the keystone of treatment, although penicillin may change the therapy of this disease.

The most frequently encountered communicable disease, the *common cold*, is not influenced by the use of the sulfonamides,<sup>4</sup> however, its bacterial complications often are. The more serious the bacterial complications, the more striking is the difference between those treated with the sulfonamides and those not treated in this manner. It is advisable not to begin sulfonamide therapy until the onset of such complications. The use of sulfathiazole combined with a vasoconstrictor drug for nasal application must still be considered in the experimental stage. The possibility of sensitization of the child to sulfathiazole must be considered although the incidence of such an occurrence is not known.

**Rheumatic Fever**—The sulfonamide drugs are either of no therapeutic value or actually seem to do harm in the acute stage of rheumatic fever, but the administration of 5 grains (0.3 gm) of sulfanilamide three or four times daily or, in the case of older children, 10 grains (0.6 gm) three times daily from October to June has proved to be very worth while in the prevention of recurrences. One author has recommended the year-around administration of sulfanilamide. It should be instituted at a time when the disease is quiescent, as determined by physical examination, leukocyte counts and the sedimentation rate. Very few children so treated have been unable to tolerate the drug. Occasional untoward reactions, of which leukopenia has been the most frequent, have shown up before the end of the first month of prophylaxis. While receiving such medication the patients should be examined at monthly intervals, at which time leukocyte counts, erythrocyte counts and determination of the concentration of the drug in the blood should be made. Sulfadiazine has been employed in the same doses as has sulfanilamide. Too few patients have been treated so far to permit an evaluation of the drug. It seems to be better tolerated than does sulfanilamide.<sup>5</sup> Sulfamerazine has been used in a few instances.

#### COMMENT

A child who is being treated with one of the sulfonamides needs extra attention. Frequent erythrocyte and leukocyte counts, urinalysis and often estimations of the concentration of the drug in the blood are necessary. Other methods of treatment should not be neglected if indicated. If this extra work is deemed unnecessary, the child is not ill enough to warrant the use of these drugs.



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## CLINICS ON OTHER SUBJECTS

### THE PATIENT COMPLAINS OF INDIGESTION

CARL G. MORLOCK

INDIGESTION or dyspepsia is a common complaint. Its importance as a factor in the health of the general population is emphasized by the number of therapeutic nostrums for digestive disorders to which the attention of the public is constantly drawn by visual and auditory advertisement. The cause of indigestion includes not only specific disease of the digestive tract, but many conditions which reflexly affect the behavior of the digestive tract. In discussing this subject it is first necessary to adopt a reasonable classification. The classification, given by Eusterman and Balfour,<sup>4</sup> is an excellent one and will be followed herein. They divided dyspepsia into four main types: organic, reflex, systemic and functional. They defined *organic dyspepsia* as that owing to organic disease of the tissues of the stomach or duodenum or of congenital or acquired anatomic abnormalities of the esophagus, stomach or duodenum. *Dyspepsia of reflex origin* is the result of disease of the appendix, gallbladder, extrahepatic biliary ducts, pancreas or intestines. The *systemic type of dyspepsia* includes that caused by systemic disease other than that in the digestive system and toxemia, disturbances of metabolism, deficiency diseases and disease of the glands of internal secretion. *Functional dyspepsia* is the result of functional gastric disturbances that do not result from demonstrable disease anywhere in the body.

The relative importance of these four main groups of dyspepsia and the frequency of indigestion in general have been clearly emphasized by Rivers and Mendes Ferreira.<sup>5</sup> In a group of 10 000 consecutive cases they found indigestion as a complaint in 42 per cent. Contrary to what might be expected, organic disease of the stomach, duodenum and esophagus was the least frequent cause of dyspepsia, in this group of cases. Systemic disease ranked first as a cause of dyspepsia, followed next by functional gastric disturbances and then by disturbances of reflex origin. Analyses by other investigators have yielded essentially similar findings.<sup>1-3</sup>

#### DYSPEPSIA, THE RESULT OF ORGANIC DISEASE OR ABNORMALITIES OF THE ESOPHAGUS, STOMACH AND DUODENUM

**Cardiospasm.**—Cardiospasm is an interesting poorly understood condition. Its etiology has never been determined accurately and it is not

certain that spasm actually is the fundamental cause. Although many patients who have cardiospasm are highly emotional and give some evidence that psychogenic trauma may be followed by the first symptoms, many other patients do not give any evidence of the nervous factor. Often the first complaint is one of slight epigastric discomfort or pain, a sense of burning, pressure or a feeling of delay in the passage of food. These symptoms may be intermittent or continuous. During the early stages an attack of epigastric pain and dysphagia may be brought on by the ingestion of coarse foods, extremely hot or cold liquids, or an emotional upset. When the condition is well established, extreme esophageal dilatation may occur and loss of weight, anemia and nutritional disturbances are common. The diagnosis usually is made readily by roentgenologic examination. The level of the obstruction is at the esophageal hiatus, the margins of the constricted portion being smooth and regular in outline. Esophagoscopy also should be done in order to exclude with more certainty the possibility of benign esophageal stricture or obstruction due to tumor.

**Tumor of the Esophagus**—Though dysphagia is the earliest and most prominent symptom in malignant tumors of the esophagus, other symptoms may occur which are suggestive of primary gastric disease. These are regurgitation, vomiting and belching. Both hematemesis and melena have been recorded. Roentgenographic and esophagoscopy examination of the esophagus will establish the diagnosis.

**Ulcer of the Esophagus**—This must still be considered an uncommon disease, though it has been reported oftener in recent years because the development of roentgenography has made its demonstration more readily possible. The cause of the lesion is somewhat in doubt. The most acceptable theories to explain its development are the presence of aberrant acid-forming gastric mucosa in the lower third of the esophagus or a patulous cardia allowing the regurgitation of acid gastric chyme into the esophagus. Either of these factors will permit constant exposure of a vulnerable esophageal mucosa to the digestive action of gastric juice, which will inevitably result in erosion and finally ulceration. The major symptom of the condition is pain located at or near the xiphoid cartilage or the retrosternal region. The pain may be referred to the back or anterior thoracic wall. It may follow the eating of solid foods and be absent when liquids are taken. Severe complicating hemorrhage and perforation of the esophagus can occur.

**Diaphragmatic Hernia**—There are many types of diaphragmatic hernia, both congenital and acquired. The symptoms are dependent on the position of the hernia, its size and the number of intra-abdom-

inal organs incorporated in the hernial sac. The para-esophageal hiatal diaphragmatic hernia, because it is the one most commonly encountered, is the only one that will be considered in this article.

The symptoms of para-esophageal diaphragmatic hernia may be complex and may be suggestive of a variety of intra-abdominal diseases. Dysphagia owing to obstruction or cardiospasm secondary to the lesion is one of the early symptoms. Sometimes considerable retro-sternal pain is experienced when food is swallowed, because of ulceration in the lower portion of the esophagus. Many patients have fairly distinct ulcer-like symptoms characterized by burning epigastric pain and relieved by the taking of small quantities of food. Because medical measures will afford much relief to many of these patients, the lesion often is unrecognized and is treated for a long time as ulcer. Hemorrhage may occur if erosion of the gastric mucosa in the hernial ring is extensive.

As the size of the lesion increases, the symptoms become those of progressive incarceration and obstruction of the stomach. At first such symptoms may be mild and consist of epigastric distress projected through to the back and relieved by the belching of gas and vomiting. Later the pain may become severe, and because of reflex spasm of the diaphragm or lower portion of the esophagus, it may be impossible for the patient to belch or vomit. Usually the recumbent position aggravates the symptoms and relief may be afforded by sitting up. Spasm of the diaphragm commonly is associated with pain in the distribution of the phrenic nerve with reference of the pain to the left shoulder and down the left arm. If the hernia becomes large, dyspnea and cardiac embarrassment may develop. If the incarceration of the stomach in the hernial ring becomes severe, pronounced obstruction and intractable vomiting may lead to dehydration and a profound disturbance of the electrolytes in the blood serum. Recognition of the condition is possible by careful roentgenologic examination.

**Achlorhydria**—Achlorhydria is a characteristic finding in patients suffering from pernicious anemia and may be secondary to progressive chronic gastritis. Many times achlorhydria is an accidental discovery in cases without any digestive disturbance whatsoever. Postprandial distress, fullness and bloating are frequent complaints, and though sometimes relief is obtained by the taking of food or some antacid preparation, at other times an equal amount of relief is obtained by the use of small doses of dilute hydrochloric acid. Troublesome diarrhea afflicting the achlorhydric patient may be corrected by the administration of dilute hydrochloric acid. It is hardly necessary to emphasize

that careful exclusion of other organic causes of bowel dysfunction is obligatory before it is wise to consider that diarrhea is due to incidentally discovered achlorhydria

**Gastritis**—This condition is being recognized as an important cause in many cases of dyspepsia that heretofore were poorly understood. The development of a flexible gastroscope which can be introduced safely and easily has played a major role in the growing knowledge of this disease. Acute gastritis may follow the ingestion of materials which are irritant to the gastric mucosa. Some of the etiologic agents which can produce acute gastritis are alcohol, salicylates, coal tar products, coarse, bulky and improperly masticated foods and thermal extremes. Symptoms attributable to this lesion are burning epigastric distress of varying degree, nausea, anorexia and vomiting. The lesion should be suspected when such symptoms follow the ingestion of a gastric irritant. The final diagnosis depends on gastroscopic confirmation.

Chronic gastritis is encountered more frequently in gastro-enterologic practice than is acute gastritis. The frequency with which the lesion is seen is subject to a wide divergence of opinion. Space permits only a brief consideration of this interesting entity. Schindler,<sup>10</sup> one of the pioneers in the study of gastritis, and co-developer of the flexible gastroscope, has divided chronic gastritis into four main types: (1) superficial, (2) hypertrophic and (3) atrophic gastritis, and (4) gastritis in the postoperative stomach.

It is hard sometimes to correlate the symptoms of chronic gastritis with the objective findings. It has been evident, since the studies of Beaumont, that a severely inflamed gastric mucosa often does not produce any symptoms. Clinical experience constantly bears out the accuracy of this original observation. On the other hand, minor degrees of mucosal inflammation often cause a great deal of distress. Some of the gastritides cause ulcer-like symptoms. This is particularly true if any considerable superficial erosion of the mucosa constitutes a part of the picture of gastritis. Such symptoms are usually irregular, they lack the characteristic periodicity of duodenal ulcer, and they are often of long duration without significant remission. Nausea may occur either before the meal or immediately after it. Loss of appetite, regurgitation and vomiting may be present. Often considerable weight is lost. When a middle-aged patient who has irregular dyspepsia loses considerable weight, neoplastic disease of the stomach may be suspected before the true nature of the condition is recognized. An associated iron deficiency type of anemia may add to the picture of possible carcinoma.

Many persons who have severe gastritis experience aggravation of

their distress by physical exertion and pressure on the abdomen. Superficial sensitivity can often be demonstrated by palpation. A massive exsanguinating hemorrhage may be a manifestation of severe ulcerative gastritis. The possibility that such a lesion is the cause of bleeding from the upper part of the digestive tract, must constantly be borne in mind if the roentgenologic examination fails to reveal a localized ulcerating lesion.

Though the diagnosis of gastritis fundamentally depends on the appearance of the gastric mucosa as seen through the gastroscope, definite presumptive evidence of the lesion can be obtained by studying the gastric secretion and the gastric sediment. In chronic gastritis of long standing there is a gradual reduction of the activity of the parietal cells with the development of relative achlorhydria. In atrophic gastritis true achlorhydria may ultimately occur, because of complete destruction of the functioning units of the mucosal glands. Mulrooney<sup>7</sup> showed that the epithelial elements and leukocytes were markedly and significantly increased in the gastric sediment of persons suffering from gastritis. The only lesion which exceeded gastritis in this regard was gastric carcinoma.

**Gastric Ulcer**—I prefer to discuss gastric ulcer separately from duodenal ulcer, even though in many respects there is a great similarity between ulcer in the two different locations, and though they are often grouped together under the generic term "peptic ulcer." Both duodenal ulcer and gastric ulcer have individual characteristics which will permit fairly accurate clinical appraisal of their probable location. Moreover, factors peculiar to each lesion lend distinction to the treatment and prognosis of each.

Gastric ulcer may be acute, subacute or chronic. Since the chronic lesion is most often encountered clinically this discussion will be confined to its appraisal. Chronic gastric ulcer may simulate chronic duodenal ulcer so closely that it may be impractical to venture an opinion as to the location of the lesion on the basis of the history alone. Characteristically the symptoms of gastric ulcer are less regular than are those of duodenal ulcer. The periodicity of the distress, so typical of uncomplicated duodenal ulcer, is lacking in a large part. Asymptomatic periods may be lacking though some remission of symptoms is characteristic. Pain usually begins within from half to one hour after the taking of food. The taking of food may give incomplete relief and indeed may aggravate it if large amounts are given. The location of the pain in the epigastrium is higher and further to the left than that of duodenal ulcer. If the lesion is large and it penetrates adjacent structures, the pain usually will be referred either

or upward into the retrosternal region. Occasional high lying gastric ulcers impinge on the diaphragm, in such cases the pain may be referred to the tip of the left shoulder via the pathway of the phrenic nerve. Gassy distress, vomiting and bleeding are characteristics of gastric ulcer. If the ulcer is in the antral portion of the stomach and involves the pylorus sufficiently to interfere with gastric motility, the symptoms will be complicated by those of obstruction. Similar symptoms will result if a mid-gastric ulcer has been present long enough to cause obstruction of the midportion of the stomach with scar tissue, in other words long enough to cause an hourglass deformity.

A competent roentgenologist will be able to demonstrate the lesion in almost every case. Presumptive evidence may be derived from a study of the gastric secretion and the demonstration of occult blood in the feces. Gastroscopic examination is of aid in evaluating the character of a gastric ulcer and indeed may demonstrate a lesion which has not been found by roentgenography.

*Differential Diagnosis of the Small Ulcerating Gastric Lesions and Malignant Tumors*—The small ulcerating gastric lesion presents a particular problem, because it requires an exact decision as to whether it is benign or malignant. It is well recognized that early gastric carcinoma may exist as a small circumscribed ulceration that is oftentimes indistinguishable, except by histologic method, from benign ulceration of equal size. Such lesions may give rise to identical symptoms.

The location of a gastric ulcer is of relative importance in differential diagnosis because experience has shown that those near the pylorus, on the greater curvature or high on the posterior wall of the stomach are more likely to be malignant than those situated elsewhere. However, though it has been stated that 73 per cent of benign gastric ulcers occur on or near the lesser curvature, the clinician should not enjoy too great a sense of security when confronted with a circumscribed ulcer in this location.

The size of the lesion is of relative assistance in reaching a clinical conclusion as to its nature. A fairly safe rule of thumb is to consider as carcinomatous any gastric ulcer with a diameter greater than 1 inch (2.5 cm) until it can be proved otherwise, however, the fact that lesions appearing to be smaller than 1 inch in diameter may be malignant must be kept constantly in mind too.

If the lesion is characterized by a classical syndrome of ulcer, the chance that it is benign is enhanced, though an irregular syndrome does not preclude such a possibility. Healing of a circumscribed gastric ulcer under adequate medical management is considered to be reliable evidence of the benignancy of such a lesion, but clinical ex-

perience has demonstrated that prompt subsidence of clinical symptoms and healing as far as roentgenographic and gastroscopic examination can determine, does not constitute positive evidence of the innocence of the lesion. Only if the lesion remains healed during an adequate follow-up period can such a conclusion be reached. The gastroscope in the hands of the expert endoscopist can give the clinician valuable aid in reaching a conclusion as to the probable histologic nature of a gastric ulcer.

Since it has been demonstrated that gastric carcinoma can be cured if the lesion can be excised in its entirety, whenever the nature of an ulcerating gastric lesion cannot be established with certainty within a reasonable length of time, early surgical exploration should be advised. It is much less dangerous to explore gastric lesions which occasionally prove to be benign, than it is to delay surgical intervention longer than is justified in order to await signs which will make possible an exact differentiation.

**Duodenal Ulcer.**—Ulcer of the duodenum is the most frequent intrinsic organic cause of chronic recurring dyspepsia. Robertson and Hargis<sup>9</sup> in a postmortem study in 2,000 cases found evidence of healed or active duodenal ulceration in about 11.85 per cent. As stated previously, certain features of the clinical manifestation of duodenal ulcer are indistinguishable from those of gastric ulcer; in any discussion in which these two lesions are considered separately, therefore, some repetition is inevitable.

Though duodenal ulcer may be an acute or subacute lesion, it is characteristically chronic and the comments in this paper, therefore, will be confined to the chronic ulcer. Chronic duodenal ulcer usually begins in the second decade of life, it often is characterized by such a typical history that it can be recognized on that basis alone. Before the discovery of roentgen rays the diagnosis of duodenal ulcer depended entirely on the interpretation of the history and able clinicians were able to obtain a high degree of accuracy in diagnosis solely by the proper evaluation of symptoms.

In the characteristic case of duodenal ulcer pain appears approximately two hours after meals in a sharply circumscribed portion of the epigastrium. The pain is described as a burning, gnawing, or exaggerated hunger sensation and is accompanied by belching, fullness and pyrosis. The pain persists until the next meal is eaten or some antacid is ingested; hence, Moynihan<sup>8</sup> spoke of the "food-comfort-pain" syndrome in duodenal ulcer. The pain characteristically recurs daily for weeks or even months, and then is followed by an interval of complete freedom from distress. These asymptomatic periods are



able duration, for they may extend for weeks, months or even years. As time goes on, the attacks of pain last longer and the intervals of remission become shorter or disappear altogether. An unexplained feature of the rhythm of the distress is its tendency to onset in the spring or fall, and to remit spontaneously during the winter and summer months. In many cases of duodenal ulcer the symptom complex does not exhibit the regular pattern just suggested. The interval between the ingestion of food and the onset of pain may be irregular and the symptoms may persist without any significant remission. For the most part, however, any disturbance in the characteristics of the clinical pattern assumed by the lesion are due to complications, either those of involvement of adjacent structures by penetration, or the result of disturbance of gastric motility secondary to obstruction at the pylorus. Symptoms attributable to associated ulceration of the stomach or severe gastritis will modify the symptoms of duodenal ulcer and indeed may overshadow them.

Sometimes in the case of subsensitive persons the presence of the ulcer is not felt until it has become deeply penetrating and is provoking intense pain stimuli. In these instances the pain may be referred to a region which derives its innervation from the same segment of the spinal cord as that which supplies the structures involved by the penetrating ulcer. The pain, therefore, may extend to the midline in the region of the lower thoracic vertebrae if the ulcer has penetrated the pancreas, or the pain may extend retrosternally and be confused with angina pectoris. The only pain experienced by many patients is that which comes on during sleep. Occasionally duodenal ulcer is manifested by sporadic attacks of severe pain, rather than the day after day occurrence of pain related to the digestive cycle. Alcoholic beverages taken when the stomach is empty may aggravate or initiate the pain of duodenal ulcer and excessive smoking may prolong the attack or increase the pain of susceptible persons. Nervous tension, excitement, undue exposure to cold, unusual physical exertion or fatigue may render an episode of pain more severe and less easily controlled. In a few cases nausea and vomiting, even in the lack of demonstrable disturbance of motility of the stomach, may be the predominant feature of an active ulcer. In a series of proved cases of active duodenal ulcer it was found<sup>5</sup> that painless bleeding, either hematemesis or melena, was the sole manifestation of the lesion in 1.5 per cent.

**Carcinoma of the Stomach**—Though the laity generally has been taught to view with suspicion any new or unusual symptom, the average patient suffering from carcinoma of the stomach does not consult his physician until his symptoms have been present for from three to

twelve months. Sometimes too the significance of mild digestive disturbances of a patient who is in middle life is not appreciated by the physician consulted. The most valuable asset to the physician in enabling him to make an early diagnosis of gastric carcinoma is eternal vigilance and a high index of suspicion toward the possibility of the presence of such a lesion. A serious hindrance to improved results in the treatment of the disease is the fact that many of the lesions have extended beyond the wall of the stomach before they cause their primary symptoms. Early diagnosis is often the result of accidental discovery during the course of a general health examination. It is a misfortune that early carcinoma of the stomach does not manifest itself more often by the symptoms of localized ulceration, while it is still a circumscribed lesion. A lesion of this kind presents the best hope for cure by surgical removal. Unfortunately symptoms are often absent until complications, such as bleeding, obstruction, secondary infection of the growth, metastasis and the constitutional phenomena of advanced disease are manifest. The clinical picture sometimes described for carcinoma of the stomach, namely that of a middle-aged patient formerly in good health who in recent months has been troubled by anorexia, nausea, regurgitation and vomiting, a patient who has lost much weight and who in all likelihood has a palpable epigastric tumor, is the clinical picture of advanced disease, which is almost certainly irremediable from the surgical standpoint.

Many of the symptoms of carcinoma of the stomach are determined by the size and position of the lesion. If the lesion is situated in the cardia of the stomach and encroaches on the cardio-esophageal orifice, dysphagia will be an early symptom. If the lesion is located near the pylorus, the motor function of the stomach will be disturbed from the outset. A small ulcerating gastric neoplasm may mimic a benign gastric ulcer even in its response to medical treatment. Such lesions, though they may appear to heal temporarily, will inevitably break down and prove their real nature.

Massive gastric hemorrhage may be an initial manifestation of the disease. Vague epigastric discomfort, fullness and burning, belching, slight cramps after a heavy meal, anorexia, nausea or actual distaste for food may be initial symptoms. Sometimes severe diarrhea is the first symptom of carcinoma of the stomach. Diarrhea may be protracted but is usually superseded by constipation as the disease advances. Occasionally the intestinal symptoms so overshadow the gastric symptoms that the colon is examined before attention is directed to the stomach as the possible source of the trouble.

The most important single diagnostic aid in malignant

stomach is the roentgenologic examination. Evaluation of the gastric acidity and the gastroscopic examination are helpful in the diagnosis of small circumscribed lesions. The chemical analysis of the stool for blood may be helpful. Experience has shown that presumptive evidence of the malignant nature of a small gastric ulcer is afforded by the persistent finding of blood in the stool on chemical test, even though the response of the ulcer to treatment seems to be favorable in other respects. Of course, this test is of no value unless all other sources of the entrance of blood into the gastro-intestinal tract can be excluded with certainty.

**Syphilis of the Stomach**—Syphilis of the stomach is a rare clinical entity and though it must be considered as a possibility in the differential diagnosis of dyspepsia found to be secondary to a deforming gastric lesion, it need not be considered seriously unless there is previous history of syphilitic infection, or serologic tests on the blood or spinal fluid are positive for syphilis. The disease occurs more often among men than among women, and when it occurs it affects patients of a younger age group than does carcinoma of the stomach. A certain percentage of cases of syphilis of the stomach have ulcer-like symptoms though the sequence is not regular and typical as in duodenal ulcer. Many patients experience epigastric pain immediately after eating. Gastric hemorrhage and acute perforation have been reported. In the advanced stage the picture is that of decreased capacity of the stomach. Roentgenographic manifestations, though not pathognomonic, are usually those of diffuse involvement of the gastric wall rather than of intrusion of the gastric lumen by a tumor.

If the lesion is suspected, a therapeutic trial of antisyphilitic treatment is a practical diagnostic aid. Although this method has its limitations, it is valuable if properly applied. If the treatment is vigorous, the lesion, if syphilitic in origin, should show definite improvement in a few weeks. Unless antisyphilitic treatment within a few weeks brings about improvement which is so marked that no doubt is left in the clinician's mind as to the cause of the gastric lesion, surgical exploration should be undertaken. It is wiser to subject a few patients who have gastric syphilis to surgical exploration than to jeopardize a patient who has carcinoma of the stomach by delaying operation too long.

#### REFLEX DYSPEPSIA

Epigastric symptoms as a primary manifestation in *acute or subacute disease of the appendix* are well recognized. Though it is conceivable that recurrent subacute appendicitis could cause a recurrent type of dyspepsia, experience has shown that this explanation for dyspepsia

should be accepted with many reservations. Rivers and Mendes Ferreira accepted appendicitis as an important cause of dyspepsia in only 2.2 per cent of the 4,223 cases which they studied. It is exceedingly unwise to attribute to appendicitis chronically recurring dyspepsia without a carefully detailed exclusion of all other possibilities, and even then appendectomy often will produce a result disappointing to the patient and the surgeon alike.

*Cholecystic disease* is a common cause of dyspepsia. Rivers and Mendes Ferreira found it second only to functional disturbances as a cause of dyspepsia among women. In addition to the characteristic acute attacks of colic, many other digestive symptoms are caused by disease of the gallbladder. There may be mild attacks of epigastric distress, a sense of fullness, bloating, pressure, regurgitation and belching. Foods high in fat and certain leafy vegetables are poorly tolerated and if eaten may precipitate an acute attack of pain. A recurrent ulcer-like distress may so closely simulate that of peptic ulcer that a differential diagnosis cannot be made without the aid of a roentgenogram. Fortunately the development of cholecystography to a high degree of efficiency has made the diagnosis of gallbladder disease a much more exact science than was ever possible by the interpretation of symptoms alone.

*Congestive or inflammatory pancreatic disease* not uncommonly occurs. Dyspepsia and pain are characteristic features of such involvement. Many times the true nature of the digestive disturbance is not suspected and it is attributed to disease of the gallbladder, stomach or duodenum. If the inflammatory engorgement of the pancreas is great, interference with the egress of bile into the duodenum may cause moderate icterus. The presence of icterus then strengthens the impression that the primary problem is disease of the biliary system. Surgical exploration usually is needed in such cases to establish the diagnosis with certainty. Sometimes duodenal deformity is secondary to inflammatory or neoplastic pancreatic disease. This deformity often leads to an erroneous diagnosis of duodenal ulcer. Sometimes a primary pancreatic neoplasm involves the duodenal wall, secondary ulceration occurs and fairly brisk bleeding into the digestive tract may result. Under such circumstances a presumptive diagnosis of hemorrhagic duodenal ulcer may be entertained before the exact nature of the lesion is recognized. Since the dyspepsia experienced in pancreatic disease is irregular and the pain occurs frequently in the left upper quadrant of the abdomen and has a tendency to secondary extension into the back, such symptoms should put the clinician on his guard as to the possibility of this lesion.

Rarely a small unrecognized *epigastric hernia* will give distress which can be mistaken for that of peptic ulcer. Disease of the small intestine and colon, particularly if causing a reverse intestinal gradient, may result in epigastric fullness, belching and postprandial distress.

#### DYSPEPSIA, THE RESULT OF SYSTEMIC DISEASE OTHER THAN THAT IN THE DIGESTIVE SYSTEM

Rivers and Mendes Ferreira found systemic disease the most frequent cause of dyspepsia in the 4,223 cases which they analyzed. Cardiac and pulmonary diseases frequently cause indigestion. *Angina pectoris* may give marked epigastric discomfort that can be mistaken for that caused by primary gallbladder disease or penetrating peptic ulcer. The patient who has a *failing myocardium* is not uncommonly seen on the wards of the gastro-enterologist, because the symptoms of epigastric fullness after meals, loss of appetite and abdominal distention are so troublesome as to overshadow the diminished tolerance to exercise and swollen ankles which are evident on closer questioning and examination.

It is well recognized that anorexia, nausea and vomiting are frequent early symptoms in *pulmonary tuberculosis*, and indeed may be manifest long before the patient's suspicions as to the presence of pulmonary disease are aroused by pain in the thorax, cough, or hemoptysis. *Syphilis of the central nervous system*, as seen in tabes dorsalis, may be the cause of severe recurrent epigastric pain and intractable episodic vomiting.

*Degenerative renal lesions* with secondary uremia, as well as *nephrolithiasis* and *hydronephrosis*, may be the cause of anorexia, nausea and vomiting. Gastric symptoms of epigastric burning, fullness after eating and loss of appetite are not uncommon in cases of *pernicious anemia*. These symptoms probably are due to the associated achlorhydria and atrophic gastritis. If they are marked and recently accentuated and the patient is obviously anemic, carcinoma of the stomach may be suspected. Gastric disturbances also may be manifest with *exophthalmic goiter* and *Addison's disease*.

#### FUNCTIONAL GASTRIC DISTURBANCES

Functional dyspepsia is common and was second in frequency to the dyspepsia of systemic disease in the group of cases studied by Rivers and Mendes Ferreira. Many gastric symptoms are due to *faulty habits of eating*. The person who eats irregularly, hurriedly and without masticating his food properly commonly suffers from dyspepsia. In many such cases simple correction of eating and living habits results in the disappearance of symptoms.

*Nervously exhausted or constitutionally inadequate persons* often suffer from visceral dysfunction which gives rise to gastro-intestinal symptoms of variable severity. Some of the symptoms described are bloating, belching, retrosternal burning, abdominal soreness and constipation. It is well known that acute mental states, such as fright, worry and anxiety, may result in nausea, delayed gastric motility, vomiting, constipation or diarrhea. It is less well recognized that nervous tension and worry of long standing may result in a complete breakdown. This breakdown may be complicated by gastro-intestinal symptoms which are severe and exceedingly difficult to overcome. Persons who have a heredofamilial background of nervous instability, therefore, should make a particular effort to guard against long-standing fatigue and the unwise expenditure of nervous energy.

Many times psychogenic gastric symptoms may be like those of ulcer or may resemble those of cholecystic disease. A mark of distinction is their daily occurrence as contrasted with the intermittent manifestations of organic gastric, duodenal or cholecystic disease. Vomiting may be hysterical or nervous in origin, or may be a marked feature in severe migraine. The absence of evidence of retention of food and the relationship of the time of emesis to the time of the ingestion of food are important factors in the recognition of functional vomiting. One functional condition may be said to constitute a definite clinical entity. This is called *anorexia nervosa* and is characterized by loss of appetite, reduced capacity for food, abdominal heaviness, distress, gas, nausea, vomiting, constipation, loss of weight and a lowered metabolic rate. This condition has been well described by Berkman.<sup>2</sup>

It is hardly necessary to emphasize the importance of a thorough exclusion of every possibility of organic disease responsible for the digestive complaints even in the most highly nervous and obviously constitutionally inadequate patient, before accepting a functional explanation for them. It is important to recognize that a nervous person who perhaps has been a lifetime sufferer from an obviously functional dyspepsia may also have organic disease. If such a dyspepsia has manifested a recent change, particular vigilance must be exercised to insure that organic digestive disease has not supervened.

#### SUMMARY

In the case of a patient who complains of indigestion the physician's responsibility does not cease when he has excluded intrinsic organic disease of the stomach, duodenum or gallbladder. It is necessary for him to remember that dyspepsia can result from disease in part of the gastro-intestinal tract and any of the accessory

organs. He also must be aware that a great number of systemic diseases may be manifest initially by gastro-intestinal symptoms and that others may produce such symptoms as the disease becomes severe. Finally the physician must be a psychologist and a psychiatrist, otherwise he not only will fail to recognize the basic causative factors in the explanation of the complaints of many of his patients who suffer from psychogenic or functional digestive complaints, but he will be totally unable to cope with the unique problem of assisting these persons in their quest for better health.

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# THE CONTROVERSIAL ISSUE OF THE USE OF DIGITALIS IN CORONARY ARTERIAL DISEASE

FREDRICK A. WHITNEY

A wide difference of opinion exists among physicians relative to the use of digitalis in coronary arterial disease. At one extreme are those who decry the use of digitalis under any circumstances while at the other extreme are those who administer the drug as part of a routine procedure. These radical therapeutic philosophies, regardless of their merits, are of less interest than the countless individual philosophies that occur between these paradoxical views. As many of these individual opinions are analyzed



foregoing experimental methods of measuring coronary blood flow after the administration of digitalis, the following factors deserve comment. The isolated ring method is obviously unphysiologic. The volume of flow from a severed superficial coronary vein is not a reliable index to the flow of blood in the coronary arteries, too many factors may change the venous flow, with or without a corresponding change of flow in the coronary arteries. The coronary blood flow in the heart-lung preparation may be altered by the effects of the preparatory operative procedure, by the anesthetic agent, and by the fact that the heart is usually denervated."

In the consideration of experimental evidence it is important to realize that the evidence obtained in normal animals under artificially produced conditions cannot be strictly applied to the human organism under pathologic conditions. In the case of the experimental animal, the heart and its coronary circulation are normal and the experiment necessitates both the employment of anesthesia and a surgical procedure, and often denervation of the heart. This status is obviously different from that in a case in which disease of the human heart has been present for a considerable time and in which the patient is not subjected to the physiologic disturbing influences of either anesthesia or operation on the heart. There also appears to be a difference in the response to digitalis in different species of experimental animals.<sup>1</sup> Furthermore, it is well known that the action of digitalis on a normal heart cannot be justly compared to its action on the diseased heart. Cognizance also must be taken of the dose of digitalis employed. Comparative interpretation of toxic doses of the drug in the experimental animal with therapeutic doses in the case of human beings with coronary arterial disease is in no manner justifiable. With these discrepancies in mind it is now possible to consider the major objections which have been expressed to the use of digitalis in cases of coronary arterial disease.

The first premise dealing with vasoconstriction of the coronary tributaries and a resulting diminution of the coronary blood flow does not find confirmation according to experimental evidence when calculated comparable therapeutic doses of digitalis are employed. This fact becomes apparent from the experimental studies of Essex, Herrick and Visscher,<sup>4</sup> Essex, Herrick, Baldes and Mann,<sup>5</sup> and Dearing, Essex, Herrick and Barnes.<sup>3</sup> These workers, in separately conducted experiments, found no appreciable changes in coronary blood flow. With toxic doses of the drug, however, a decrease in coronary blood flow occurred and persisted from four to six hours after the drug had been administered.

Again, presupposing the correctness of the belief that the results of animal experiments cannot be positively correlated with clinical states, the data in question must be subjected to clinical analysis. This has been done countless times, both wittingly and unwittingly, by the medical profession. While clinical observations lack certain precision possible in experimental studies, they, nevertheless, when carefully made and recorded, justify certain practical conclusions. Generally speaking, clinicians are agreed that older patients, especially when congestive heart failure and auricular fibrillation and flutter do not exist, are less tolerant to the action of digitalis than are younger patients, particularly when the latter display the above mentioned exceptions. Digitalis intoxication, particularly the toxic cerebral manifestations (giddiness, disorientation, hallucinations, disturbances in color vision, coma and death) occur more commonly among patients of the older age groups, especially when the drug is administered rapidly in accepted average dose and when its administration is continued for relatively long periods of time even in small doses. While coronary arterial disease is by no means limited to the older age groups, its occurrence after the age of fifty years is remarkably frequent.

From time to time patients with the anginal syndrome of coronary disease without evidences of congestive heart failure are encountered who have received or are receiving digitalis in moderate doses. Many of them volunteer the information that the frequency of the anginal attacks increased with the administration of the drug and that the seizures became less frequent after digitalis therapy had been discontinued.

Regardless of the nature of a specified cardiopathy, when congestive heart failure has not occurred or does not appear imminent, and when the cardiac rhythm is regular and the heart is not greatly enlarged, the advisability of more or less continuous digitalis therapy even in small doses is open to considerable question.

The second premise presupposing the danger of producing regions of myocardial necrosis by the administration of digitalis is integrated in the presumptions expressed in the first premise. Here again the evidence obtained was derived from animal experimentation in which toxic doses of digitalis were administered. This problem was also investigated by Dearing and his co-workers<sup>7</sup> who found no demonstrable changes in the myocardium after administration of either 40 or 50 per cent of the minimal lethal dose of digitalis. When the dose was increased to 70 or 80 per cent of the minimal lethal dose, the frequency of cellular changes in the myocardium increased. These lesions occurred more frequently in older than in younger animals. I have been

unable to find any authentic instance of the production of focal myocardial necrosis in the human heart by the administration of digitalis

From the experimental evidence at hand, together with clinico-pathologic experience relative to the human heart, no evidence exists that myocardial necrosis is a genuine hazard in digitalis therapy, and certainly not when toxic phenomena are avoided

The final premise, namely, the belief that profound disturbances of ventricular rhythm, such as ventricular tachycardia and ventricular fibrillation, are more likely to occur under administration of digitalis is definitely presumptive when applied to man. In the experimental studies of Travell, Gold and Modell,<sup>9</sup> on cats, the effect of digitalis was investigated three weeks after ligation of a coronary artery. They found that all the animals were more susceptible to the drug than the normal controls and that the amount of digitalis required to produce ectopic ventricular rhythm and death was only three-fourths the amount required to produce similar effects in the control animals. These investigators suggested the possibility that digitalis favors the production of abnormal impulses in the region of myocardial infarction and that these impulses are capable of precipitating attacks of ectopic ventricular rhythm.

The translation of these experimental data to clinical cases of coronary arterial disease is open to question. It is a well-known fact that both ventricular tachycardia and ventricular fibrillation occur in obliterative coronary sclerosis and in acute myocardial infarction but in the latter condition they do not occur with the frequency presumed by some authors. The actual incidence of ventricular fibrillation is not known but is probably a frequent preterminal mechanism in many fatal cases. Only continuous electrocardiographic observation preceding and during death can settle this question. Limited studies of this character have confirmed this idea.<sup>7-10</sup> Examples of ventricular tachycardia occurring during the course of digitalis therapy are recorded in the literature.<sup>6-8</sup> However, the rarity of this complication strongly suggests its occurrence only as a casual manifestation of digitalis intoxication.

In the preceding consideration there has been no intention to minimize the importance or the value of experimental observations. There has, however, been a deliberate intention to warn against the literal translation of experimental data to the noncomparable status that exists in the diseased human heart. In the consideration of any drug it is extremely important that its known actions are fully appreciated because if this cardinal knowledge is not understood its intelligent use cannot be anticipated. Even though digitalis is one of the oldest car-

diac remedies it has been sadly misused. A historical survey of this subject brings forth some amazing revelations. Even today, in the hands of many practitioners, the mere suspicion of heart disease seems to warrant its administration. While during the last two decades very encouraging progress has been made and a better understanding of the indications and contraindications of the drug has become evident, instances of therapeutic indiscrimination occur far too often.

Early in this consideration I stated my belief that somewhere between the extremities of the therapeutic philosophies a suitable answer to the problem could be found. I therefore wish to record my own opinion and that of other clinicians regarding the indications and contraindications for the administration of digitalis in cases of disease of the coronary arteries.

#### INDICATIONS

The presence of congestive heart failure or evidence of its imminent supervention constitute the chief indications for digitalis therapy in coronary arterial disease. Even here the drug must be administered cautiously, as it is well to recall that patients with this form of cardiopathy are less tolerant to digitalis than are patients with other forms of heart disease. Unless the onset of the failure is precipitous and severe, it seems justifiable, from abundant clinical experience, to resort to complete rest and the use of the mercurial diuretics before hastening to use digitalis. In cases in which cardiac function has been restored to the point of permitting a restricted ambulatory mode of life, the regular intermittent administration of digitalis for protracted periods of time is commendable. However, the use of digitalis should always be cautious and carried out under strict supervision so that any symptoms and signs of intolerance may be readily detected and the necessary countermeasures taken.

#### CONTRAINDICATIONS

1. The anginal syndrome of coronary disease without previous or existent congestive heart failure.

Toxic doses and, in certain cases, even average doses of digitalis are capable of causing the painful seizures to occur more frequently and with less provocation.

2. Coronary occlusion with acute infarction of the myocardium but unaccompanied by congestive heart failure.

3. Healed infarction of the myocardium without previous or existent congestive heart failure.

4. Coronary sclerosis with impairment of ventricular conduction.

(delayed A-V conduction, complete heart block and bundle branch block) without previous or existent congestive heart failure

5 The mere suspicion of disease of the coronary arteries (often based on the presence of pain in the left side of the thorax)

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# DIURETIC EFFICACY OF ORAL ADMINISTRATION OF A PREPARATION OF MERSALYL AND THEOPHYLLINE IN CASES OF CONGESTIVE HEART FAILURE

HADDON M. CARRYER AND HARRY L. SMITH

In the treatment of congestive heart failure the problem of administering diuretics must be considered. The efficacy of mercurial diuretics when given intravenously is well known. Occasionally, however, difficulties arise because the patient is obese, has small veins or objects to intravenous administration of these drugs. Such difficulties may deprive the patient of a valuable aid in the treatment of this disease. Because of this problem, we have attempted to evaluate the diuretic effects produced by the oral administration of a preparation of mersalyl and theophylline (salyrgan-theophylline) and have compared them with the known valuable effects of the drug given intravenously.

For oral administration mersalyl and theophylline are supplied in the form of enteric coated tablets, each of which contains 0.08 gm. of mersalyl and 0.04 gm. of theophylline. In a study similar to the one we have undertaken Dickens<sup>2</sup> administered this preparation orally in nine cases of congestive heart failure. He gave five tablets in the morning and repeated this dose at intervals of from four to six days. As many as three doses were employed in some cases. Satisfactory diuresis was produced in all cases without any serious toxic reactions.

Batterman, DeGraff and Rose<sup>1</sup> administered salyrgan-theophylline orally in twenty-nine cases of congestive heart failure and concluded that it was a safe and effective diuretic. They too used a dose of five tablets in the morning. This dose was repeated at intervals of from three to five days. As many as five doses were administered in some cases. These authors were impressed by the slowness of onset of the diuresis and by the prolonged effect. They concluded that the diuretic effect of the oral administration of the drug was not as great as that produced when the drug was used parenterally.

## CASES STUDIED AND RESULTS

The present paper is based on a study of the diuretic effect of salyrgan theophylline administered orally in twenty-two cases of congestive heart failure. The types of heart disease encountered in these cases were as follows: hypertensive heart disease in seven cases, arteriosclerotic heart disease in eight, arteriosclerotic and hypertensive heart

disease in two, rheumatic heart disease in four and heart disease associated with emphysema in one case. The severity of the heart disease was sufficient to warrant placing the patients in the hospital. All of the patients either had been digitalized before they were admitted to the hospital or received full therapeutic doses of digitalis in the first few days after they were admitted to the hospital. Other medication that appeared to be indicated was employed. When patients were seriously ill, a solution of dextrose and aminophylline was administered intravenously on the first few days that they were in the hospital. No other xanthine diuretics were given. Otherwise, the treatment was the same in all of the cases. The patients were kept in bed, oxygen therapy was employed when needed, the ingestion of salt was limited and the ingestion of fluids was restricted to 1,500 cc daily.

In order to compare the relative diuretic efficiency of the oral and intravenous methods of administration of this drug, both methods were employed in this group of cases. For intravenous use, we employed salyrgan-theophylline solution, each cubic centimeter of which contains 0.1 gm of mersalyl and 0.05 gm of theophylline. For oral administration, we employed salyrgan-theophylline enteric coated tablets,\* as described previously. When the drug was given intravenously, 2 cc of salyrgan-theophylline solution usually was administered but on three occasions a dose of 1 cc was employed. When it was given orally, five tablets were used as a single dose in the morning except on two occasions when doses of two tablets each were administered three times during the day. The intake of fluid, urinary output and weight of the patient while the patient was in the hospital were recorded daily.

Regardless of the method of administration, the maximal diuretic effect was observed within the first twenty-four hours after the drug was administered. This effect was especially noticeable during the first twelve hours. In those cases in which the presence of edema warranted strenuous diuresis, we employed the drug as frequently as every other day if urinalysis and determination of the concentration of blood urea indicated that the renal reserve was adequate.

If the difference in the absorption of the drug when it is given orally and intravenously is considered, the doses that were administered orally seem roughly comparable to those that were given intravenously. Whenever it was feasible, these two methods of administration were employed alternately in each case in order that individual variation of the response might be taken into consideration. In nineteen of the cases, the drug was first administered intravenously.

We have listed the average intake of fluid, output of urine and loss

\* These tablets were kindly supplied by the Winthrop Chemical Co., Inc.

of weight following the use of the two methods of administering the mercurial diuretic under consideration (tabulation) These figures represent data from both the day on which the drug was administered and the day following use of the drug The loss of weight and the output of urine both were greater when the drug was given intravenously than when it was given orally The tendency of the drug when administered orally to produce loose stools should be remembered when the urinary output is considered, for it is likely that fluid loss is greater than the urinary output indicates.

The oral method of administration was employed forty-seven times in the twenty-two cases and the intravenous method, sixty-six times The patients were improving gradually during the course of their hospital care and with this improvement a decreasing response was noted to all diuretics employed One of the most satisfactory types of pa-

THE EFFECT OF SALYRGAN-THEOPHYLLINE IN CONGESTIVE HEART FAILURE

Day of Observation	How Administered	Average Fluid Intake Cc.	Average Urine Output, Cc.	Average Loss of Weight, Pounds
Day of administration of salyrgan theophylline	Orally	1301	1415	1 85
	Intravenously	1294	2326	3 93
Day after administration of salyrgan theophylline	Orally	1319	1069	0 45
	Intravenously	1309	1155	0 64

tients treated was the relatively young patient who had hypertensive heart disease and was experiencing his first cardiac failure, which was commonly a fulminating affair In this type of case the best results were observed

It is our opinion that when severe edema is of recent onset and the patients are young and have adequate renal function, the oral preparation approaches the efficacy of the intravenous preparation Conversely as the age of the patient increases, as the duration of heart failure becomes longer and as the renal reserve becomes less, the diuresis obtained by the orally administered preparation is less pronounced than is that by the intravenously administered drug To state this conclusion differently—in cases in which edematous fluid is easily removed the oral preparation approaches the intravenous one when fluid is not easily removed, the results following administration far surpass those following oral administration



Few toxic manifestations, none of which were of a serious nature, were observed following the oral use of the salyrgan-theophylline preparation. Five patients experienced gastro-intestinal disturbances, with three to five loose stools a day during the period following administration of the drug. Two of these patients likewise had emesis. Several additional patients complained of epigastric burning which was promptly relieved by taking of milk. No evidence of renal irritation was noted. No untoward reactions were observed after intravenous administration of salyrgan-theophylline.

In conclusion, it may be said that while salyrgan-theophylline administered orally is much less efficient as a diuretic than the same drug given intravenously, it does represent an adjunct in the treatment of congestive heart failure, especially when for some reason a mercurial diuretic cannot be employed intravenously. Its use in the manner described was followed by no toxic manifestations of consequence. It would be a great boon to the medical profession if some drug could be developed which would act as effectively when given orally as salyrgan-theophylline does when it is given intravenously. To date, no such drug is known.

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## THE CLINICAL OCCURRENCE OF EOSINOPHILIA

J M STICKNEY AND FRANK J HECK

EOSINOPHILIA occurs in a wide variety of diseases, in some of which the increase in percentage of eosinophils can be explained on a common etiologic basis. In other diseases, however, no causal factor is as yet accepted.

The nuclei of eosinophils of human beings are usually bilobed, only occasionally are they trilobed. The cell body contains large, uniformly round granules which have marked affinity for acid dyes. As a rule the number of granules is uniform. A single exception in our experience was one case in which, although the nuclei of all the eosinophils studied were normal, in some cells the number of granules was reduced. However, no instances were noted in which there were immature or "unripe" granules—that is, granules which were basophilic or polychromatophilic.

In the bone marrow of human beings the eosinophils are derived from cells known variously as stem cells, lymphoidocytes, myeloblasts, hemocytoblasts and so forth, and they evolve through a series of fairly definite stages. In the early stages a few basophilic or polychromatophilic granules may be present. The diameter of the granules is strikingly uniform in contrast to the great variation in size of the granules of basophils. In addition to the formation of eosinophils in the bone marrow, tissue eosinophils are derived from various sources. Of these latter, lymphocytes, large mononuclear leukocytes, plasma cells and adventitial cells are regarded as parent cells.

Practically all experimental studies on the origin of the eosinophil or of the granules of the eosinophile leukocyte point to the importance of anaphylaxis. While originally the eosinophile granule was considered to be formed from the erythrocyte or from erythrocyte degeneration products, this viewpoint has been shown to be incorrect. Subsequent investigators agree rather uniformly on the role played by protein sensitization in the origin of eosinophils. Investigators found that a single injection of suspensions of erythrocytes, hemoglobin or egg albumin did not increase the number of eosinophile leukocytes in the blood. However repeated injections of these materials at intervals of eight to twelve days resulted in marked increase in eosinophile leukocytes in the blood stream and in the peritoneal cavity. Experimentally eosinophilia has been noted after injections of pilocarpine, inoculation

with *Trichina*, injection of extracts of *Taenia solium* or injection of aqueous extracts of *Ascaris lumbricoides*

The clinical significance of eosinophilia, in which more than 6 per cent of the leukocytes in the circulating blood are eosinophils, has been considered at length in the literature. It is universally agreed that certain diseases and conditions are frequently associated with eosinophilia of this degree, but in different studies the relative incidence of eosinophilia in any one disease has varied a great deal. Eosinophilia is a common finding in (1) asthma, hay fever and vasomotor rhinitis, (2) parasitic infestation, especially that of the intestine, (3) dermatoses, especially the type in which allergy plays a role and (4) blood dyscrasias and lymphoblastoma.

The number of conditions in which eosinophilia may be observed occasionally is greater. In this group authors frequently mention (1) malignant lesions of all types, (2) periarteritis nodosa, (3) postfebrile debility, (4) starvation, (5) syphilis, (6) administration of digitalis, (7) polymyositis, (8) pleural effusions in which there are many eosinophilic leukocytes and (9) benzene and nirvanol poisoning. In addition, the ingestion of raw liver and the parenteral administration of liver extract occasionally are followed by eosinophilia. Also, transient pulmonary infiltration, frequently in the apical areas, may be accompanied by eosinophilia.

We have analyzed the experience of the Mayo Clinic in a group of 418 cases in which 6 per cent or more of the leukocytes in the blood were eosinophils. The percentage distribution of diseases in association with various degrees of eosinophilia is shown in the accompanying tabulation.

From our study we have concluded that, with few exceptions, the degree of eosinophilia is of little importance in differential diagnosis.

The low incidence of *parasitic infection* in each group is explained by the fact that few cases of active parasitic infection are seen at the Clinic. The experience of other investigators in a different type of practice indicates that parasitic infection may be the leading cause of eosinophilia. This is especially true of acute trichinosis.

*Allergic disease of the respiratory tract* is commonly associated with eosinophilia and in our experience is the most common cause. Differential blood counts in which from 6 to 77 per cent of the leukocytes in the blood stream were eosinophils were found in this group of diseases and the number of cases was fairly evenly distributed through the whole range. In cases of vasomotor rhinitis it is well known that there may be a local increase in number of tissue eosinophils.

Our experience with the *dermatoses* is similar to that of others.

Eosinophilia of low or high degree may be found in cases of eczema, pemphigus, dermatitis herpetiformis, mycosis fungoides and dermatitis medicamentosa

*Infections* of many types, both acute and chronic, are to be considered in the presence of eosinophilia. We have found eosinophilia in cases of acute appendicitis. There appears to be little correlation between the occurrence of eosinophilia in the appendix and the eosino-

DISEASE PRESENT AND PERCENTAGES OF EOSINOPHILS IN THE CIRCULATING BLOOD IN 418 CASES IN WHICH EOSINOPHILIA WAS PRESENT

Disease	Per Cent of Eosinophils		
	6-10	10-20	20+
	(Per Cent of Cases)	(Per Cent of Cases)	(Per Cent of Cases)
Asthma, hay fever and vasomotor rhinitis	33	44	28
Nonparasitic infections	19	12	11
Blood dyscrasias and lymphoblastoma (leukemia excluded)	5	8	20
Dermatoses	7	9	10
Parasitic infections		3	4
Malignant lesions	5	3	4
Periarteritis nodosa			10
Miscellaneous	31	21	13
Total	100	100	100

philia of the blood. Chronic ulcerative colitis is one of the chronic infections frequently seen at the Mayo Clinic and may be associated with eosinophilia of almost any degree (51 was the highest percentage of eosinophils in our series). In all cases, parasitic infection has been ruled out. In several cases chronic cholecystitis and chronic infectious (rheumatoid) arthritis were found to be accompanied by eosinophilia.

If there is any special factor causative of eosinophilia in the presence of the various *malignant lesions* in which eosinophilia was present, it may be metastatic involvement of the liver since this occurred several times in our experience.

Eosinophilia may be associated with several diseases in which the reticuloendothelial system is involved. This statement is especially true

of *chronic myelogenous leukemia*, in which the total number of eosinophils is commonly increased. In 75 per cent of 200 cases of chronic myelogenous leukemia which are not included in the present study, 6 per cent or more of the leukocytes in the circulating blood were eosinophils. The highest percentage of eosinophils in this series was 51.5. More marked eosinophilia than this, however, does occur in association with chronic myelogenous leukemia. We do not recognize eosinophilic leukemia as a separate entity but rather group all our cases, regardless of the predominating type of mature myeloid cell, under the single heading of chronic myelogenous leukemia. Immature eosinophils are rarely in the blood in any disease other than myelogenous leukemia. Cells poor in granules also may be seen in cases of myelogenous leukemia. Eosinophils with basophilic or polychromatophilic granules seldom are found in conditions other than chronic myelogenous leukemia.

*Lymphoblastoma* of various types is the other disease of the reticulo-endothelial system in which eosinophilia is of common occurrence. In approximately 15 per cent of a series of 100 cases of lymphoblastoma, 6 per cent or more of the leukocytes in the circulating blood were eosinophils and in some cases more than 50 per cent were eosinophils.

*Periarteritis nodosa* has been of particular interest to us. It is usually stated that eosinophilia is present in about 15 per cent of cases of this disease. In our experience with cases in which the diagnosis of periarteritis nodosa has been confirmed by a pathologist, we have found this incidence too low if the entire course of the disease is considered. The association of asthma and eosinophilia of high degree with a progressive febrile illness, if the patient is a young adult, should arouse the interest of the clinician in this diagnosis. Many features point to allergic factors in the cause of eosinophilia in this disease.

The miscellaneous diseases included in our study presented little that seemed significant with respect to eosinophilia. There were several cases of *cirrhosis of the liver* and it may be significant that any process which destroys the substance of the liver often is associated with eosinophilia. Another interesting observation is that in many cases in which *chronic nervous exhaustion* was the only diagnosis that could be made eosinophils were present in excessive numbers in the blood. We have not been able to identify an eosinophilic pulmonary infiltration (Loeffler's syndrome) among our cases.

When eosinophilia is encountered, the problem which confronts the clinician is to consider the common causes and, if no cause can be found, to determine whether the degree or persistence of the eosino-

philia is in itself a significant factor in making a diagnosis. Eosinophilia in excess of 20 per cent would seem to have little more significance than eosinophilia of a lesser degree except that the possibility of periarteritis nodosa or a blood dyscrasia being present may be greater in the presence of the higher percentage of eosinophils. The daily, and perhaps hourly, variation in the eosinophils is considerable and may alter the importance of the findings.

# INTERPRETATION OF THE PERIPHERAL WHITE BLOOD COUNT

MALCOLM M HARGRAVES

THE white blood count should be a tool in the hands of every practicing physician to obtain information helpful to his patient. The full worth of the information so obtained then depends on the interpretation placed on it. This paper is a consideration of factors which may be useful in such an interpretation.

It would seem superfluous to say that one's information should be accurate but accuracy is often difficult to obtain. Standardization of equipment and technic is of the greatest importance. Bureau of Standard pipets and counting chambers, or their equivalents, should be used. Equipment should be chemically clean. Diluting solutions should be fresh and accurately compounded. A free-flowing drop of capillary blood should be obtained by a uniformly deep puncture wound and all preparations should be made in an unhurried but rapid manner. Practice in developing a uniform technic will pay dividends in accuracy.

Since the stained blood smear is so important in interpretation, great care should be exercised in preparing it on chemically clean glass slides or coverslips. With practice and patience a fairly uniform smear can be made with areas very satisfactory for study and differential counting. It should be dried rapidly by waving it through the air to prevent crenation or shriveling of the blood cells. It should then be stained by a technic which will give a uniform preparation, so familiar to the examiner that variation of structure, granulation and staining reactions can be detected.

It must be recognized that there is error inherent in the method used for blood count determinations. Berkson, Magath and Hurn<sup>1</sup> have shown that with all factors standardized as much as possible there is still a plus or minus error of 21 per cent in the white blood cell count and a plus or minus error of 16 per cent in the red blood cell count. When one realizes the number of variables introduced in taking the average blood count, the desirability of making two or more determinations is obvious, particularly when the count is important for diagnostic or treatment needs.

One's thinking on the matter of numbers of circulating blood cells must be *physiologic* if one is to make sound interpretations. One must

cease to consider the circulating population of the blood stream as a fixed, static one but rather consider it as a shifting, dynamic group of cells ever changing to meet the needs of the body. During periods of health the production of white blood cells in the bone marrow is essentially equal to the needs of the body and this state of equilibrium yields a relatively stable count varying around 7,500 per cubic millimeter of blood. When conditions within the body change to upset this equilibrium, one gets quantitative and qualitative changes which must be interpreted to evaluate the physiologic activities taking place.



means of interpreting bone marrow and tissue activity Cells younger than the metamyelocytes are seen in the peripheral blood only under unusual circumstances The metamyelocyte is probably the youngest functional cell of the myeloid series with its indented nucleus, full complement of cytoplasmic granules and active motility As this cell matures, lobes develop in the nucleus These are joined by a fine filament containing no chromatin material The nucleus probably acquires successive lobes in an orderly fashion as it ages Accepting this hypothesis, numerous ways of expressing the age of these cells have been devised Each of these has its usefulness depending on the experience of the interpreter Since most charts show the younger forms at the left with succeeding ages to the right, a common expression has arisen that indicates the comparative maturity of the cells, that is, a "shift to the left" indicates that there are more young cells in the differential count than in the accepted normal hemogram or in previous successive counts used for comparison A "shift to the right" obviously means that the cells are more mature than those used for comparison

The *Schilling*<sup>0</sup> *hemogram* is in common use for expressing this age of granulocytes although the "*filament-nonfilament*" count<sup>3</sup> is gaining in frequency of use because of its simplicity It is quite easy in clinical work to classify the neutrophils, while one is doing the differential count, into "filament" forms, or older cells whose nuclei have formed lobes connected by a fine filament, and "nonfilament" forms or the younger nonsegmental cells If the criterion of Cooke and Ponder<sup>2</sup> is adhered to, that is, that the filament must not contain any chromatin material but be only a fine strand, then the personal element of judging which is or is not a filament form is eliminated and counts by different workers can be used for comparison and interpretation The acceptance of this criterion is extremely important if the method is to be trustworthy An elaboration of the filament-nonfilament count can be used for more scientific work and lends itself to the charting of successive counts This is Cooke and Ponder's "weighted mean," which is the mean of nuclear lobes per cell I have used the same method of actually counting the number of lobes in 100 neutrophils and using this number as a "lobe index" which theoretically would show as fine a variation of age change as one lobe in 100 cells This gives a round number which can be easily charted

The *study of the blood smear* will give additional information to one experienced in its examination under conditions of uniform preparations and staining technic Numerous "toxic manifestations" are observed, one of the most common of which is "toxic granulation" in the neutrophil<sup>7</sup> In this condition the neutrophilic granules become

swollen and dark staining, the cell standing out prominently as a "toxic cell" damaged by the septic process of the patient. The number of these "toxic granule" cells bears a relationship to the severity and type

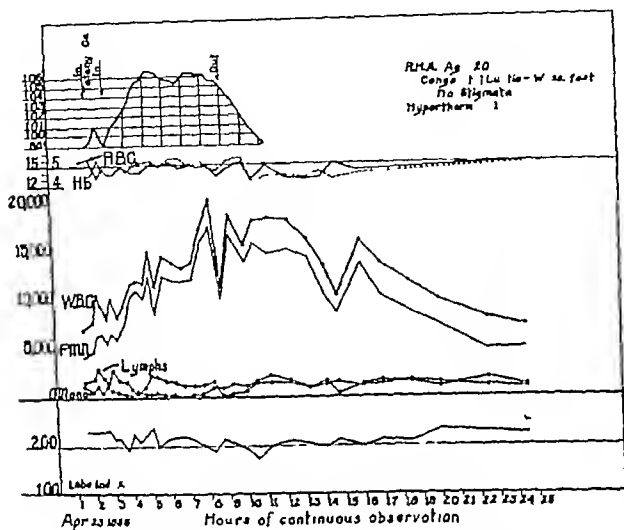


Fig 69—The leukocyte response to artificially induced fever therapy. Note that the total count is not a uniform type of curve. While this may in part be explained by technical error inherent in counting irregularity of bone marrow delivery of cells is probably a factor. It will be noted that as the leukocytes increase in number they are primarily made up of neutrophils and there is some fall of absolute numbers of both monocytes and lymphocytes. The lobe index indicating the number of lobes in 100 neutrophils expresses a shift to the left in nuclear pattern by its fall. With the foregoing leukocytosis made up primarily of neutrophils, there is a progressive fall of the lobe index indicating bone marrow delivery of younger cells. After fever therapy and with a fall of the temperature, the leukocyte count slowly returns to normal with a rise of the lobe index to normal, indicating a state of equilibrium between bone marrow delivery and tissue demands for leukocytes. It will also be noted that as the leukocyte curve declines, the fall of the number of neutrophils is more rapid than that of the total count since a developing monocytosis and later lymphocytosis help to sustain the total count.

of infection. Rosenthal and his associates<sup>5, 10</sup> have published a number of papers on the clinical application of this datum. The advent of sulfonamide therapy has somewhat obscured its usefulness since the drugs themselves often produce toxic granulations at higher levels of con-

centration The type of organism also seems to alter the degree of toxic granulation, the pus-forming group giving a great deal and the streptococci considerably less

In severe infections Dohle's inclusion bodies are often seen in the cytoplasm These are probably condensations of the bluish basophilic spongioplasm They seem most common in streptococcal infections

Degenerative nuclear changes are also of importance with condensation of the chromatin, bizarre nuclear shapes and nuclear vacuoles Phagocytic activity, particularly with supravital preparations, can often be seen in any of the cells except the lymphocytes

With this short summary one then has information for better interpretation of the peripheral white blood picture as it applies to the individual patient Let us analyze a leukocytosis curve (Fig 69) as it is induced by a five hour session of artificially induced fever therapy with body temperature maintained around 106° F for this period\* Essentially the same type of leukocyte picture is produced with the first malarial chill and the intravenous injections of typhoid vaccine and I have every reason to believe from observation that bodily infections and trauma (burns, contusions, hemorrhages, and so forth) would give comparable pictures if one were only fortunate enough to be able to follow the process from the onset

#### LEUKOCYTE PICTURE WITH ACUTE PROCESS

It should be said at this point that profound, temporary leukopenia usually occurs if the patient has a chill Evidence would indicate that this is entirely a redistribution phenomenon in which there is an accumulation of cells in the visceral circulation and a paucity of cells in the peripheral circulation This is probably secondary to vasomotor changes and peripheral vasoconstriction with no qualitative changes in the cells themselves

In the initial period of tissue injury there may be a slight drop of the peripheral white blood count as the cells leave the circulation and go into the region of tissue damage As the tissue demand for more cells is made there is a rise of the total white blood cell count as the bone marrow releases its reserves These reserves are made up primarily of neutrophils which have been maturing in the bone marrow and there may be little shift to the left in the nuclear pattern at this stage,

\*I have been interested in this problem for the last ten years and much of the interpretation of blood counts is based on the leukocyte changes produced by fever (Kettering hyperthermia, intravenously administered typhoid vaccine and malaria inoculation) This work was done jointly in the Ohio State Medical Research Department with Dr Charles A Doan, Professor of Medicine and Director of Medical Research, and many of the data are yet unpublished

but as greater numbers of cells are released and the total count increases there is more shift to the left. During this period of developing leukocytosis the lymphocytes and monocytes decrease. As time goes on, however, there is an increase of monocytes which is probably an expression of tissue response to damage rather than bone marrow response. Pneumonia, peritonitis and inflammatory lesions, particularly in the resolving stage, give a monocytosis which helps to keep up the

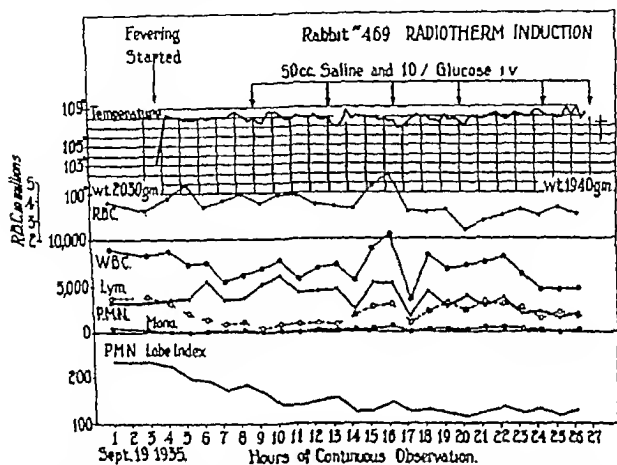


Fig 70—The leukocyte response of a rabbit fevered continuously until death. It will be noted that over the entire twenty six hour period there was no leukocytosis. In fact, the total count tends to fall. The lobe index progressively falls indicating continued delivery of younger cells from the bone marrow. This combination would indicate that the leukocytes are rapidly leaving the peripheral circulation to meet tissue needs and that the bone marrow is actively producing cells. The marrow however, is not keeping pace with tissue demands. Postmortem examination showed extensive infiltration of leukocytes into all tissues with a hyperplastic bone marrow (From M. M. Hargraves and C. A. Doan. Unpublished data.)

leukocytosis as the number of neutrophils is falling. If the process is coming under control, this falling of the neutrophilic curve is accompanied by a shift to the right toward normal in the nuclear pattern. This period is also represented by developing lymphocytosis.

In acute infections there may be a failure of leukocytosis to develop, even with successive counts (Fig 70). This may be true particularly in cases of acute infections of the abdomen and the attending phys-

ician may be baffled by this seemingly normal leukocyte count. The qualitative changes in the cells, however, are the crux of the problem and successive counts show a progressive shift to the left as the bone marrow throws younger cells into the peripheral blood. These cells do not accumulate and produce leukocytosis because they leave the circulation too fast. (It must be admitted that the leukopenias, such as in the virus infections, are probably not explained on this basis but are due to bone marrow suppression.) In severe infections it is fairly common to find a leukemoid reaction in which the bone marrow releases all available cells and even the immature ones are being swept into the peripheral circulation. In overwhelming sepsis there is fairly commonly a progressive fall of total count accompanied by a progressive shift to the left, indicating that the bone marrow cannot keep pace with bodily needs.

#### LEUKOCYTE PICTURE WITH CHRONIC PROCESS

What has been said about the leukocyte picture with an acute process applies to the chronic infectious state in part. It is, however, modified by chronicity. With changing tissue demands the count will vary to meet these needs but the toxic changes in the cells alter the interpretation of qualitative changes. This is particularly true when one attempts to apply the criteria of age of cells as indicated by their shift to the left. The toxic degenerative nuclear changes alter the configuration of the nuclei, which no longer acquire successive lobes in an orderly fashion as previously noted. Instead the cells tend to become stab forms with the nucleus staining quite darkly, owing to condensation of the chromatin. Instead of lobules connected by a filamentous strand such as one sees in normal cells, the nucleus becomes contorted with abortive lobules connected by constricted regions containing chromatin. Irregularities of contour also develop in the nucleus. These suggest pseudopods or miniature side lobes connected to the main nucleus by a filament. There is also a tendency for the nucleus to become vacuolated and these vacuoles often push to the periphery of the nucleus, particularly in the Hof, with the formation of filamentous appearing strands made up of the nuclear membrane. In fact in many of these cells this nuclear Hof appears to develop by the confluence of many of these vacuoles.

Under such circumstances a filament-nonfilament count is of little importance except that it will advise the observer that the leukocyte picture is abnormal. It may not give any insight into bone marrow delivery of cells. In such a case in which there has been chronic disease with almost continuous stimulation of the bone marrow for ex-

tended granulopoiesis, leukocytosis will often be greater with an acute process than if the marrow were normal. For example, in a case of gonorrheal arthritis there have been fever and more than 40,000 leukocytes per cubic millimeter of blood but very little change of the lobe index. The lobe index in this type of case is very low to begin with because of these degenerative nuclear changes. Examination, however, of the blood smear will advise one of these qualitative changes and still permit one to include it in the pattern of response.

### COMMENT

From this consideration of the physiologic and morphologic factors involved in the leukocyte count and with the postulation of a pattern response that has just been described, one is in a position to evaluate the individual leukocyte picture more fully by attempting to fit it into its place in this pattern. Such a procedure must take cognizance of the time of onset of illness, particularly with respect to a chill, previous state of health of the patient, probable type of organism involved and the duration of the illness. With such information one is in a better position for adequate diagnosis, treatment and prognosis than without it.

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# MALINGERING, WITH REFERENCE TO ITS NEUROPSYCHIATRIC ASPECTS IN CIVIL AND IN MILITARY PRACTICE

FREDERICK P MOERSCH

FEW medical situations tax the patience and the ingenuity of the physician more keenly than his contact with the malingerer. This statement applies to all physicians, as no branch of medicine escapes the malingerer's broad field of activity. To the newly appointed medical officer it may appear that malingering is more common in the life of the soldier than in the life of the civilian. This is an impression that need not be true. The impression results from the medical officer's close contact with large groups of men hastily recruited and among whom psychologic reactions are precipitated by the sudden readjustments necessitated by military service. The malingerer would seem to be of concern primarily to the neuropsychiatrist. This is probably correct. As pointed out by Waud<sup>10</sup> and others, if it is at all possible, the person suspected of malingering should have a neuropsychiatric examination. However, every physician should accept the responsibility of dealing intelligently with such a person. This is especially true if the symptoms of which the suspect complains are in that physician's special field of activity. In this discussion I am concerned with the malingerer primarily from the neuropsychiatric standpoint and cannot enter into a discussion of the diverse symptoms of malingering in reference to the various bodily functions except as they have some special neuropsychiatric implication.

## HISTORICAL

A great deal of the early literature on the subject of malingering refers to "feigned disease" in relation to military service. This military connection probably resulted from the fact that many of the early works on the subject came from the pens and hearts of naval and army surgeons who wrote feelingly and frequently on malingering. Military surgeons were fully aware of the cheats who would cut off a thumb or a finger to avoid military duty. They recognized the imposters who feigned blindness, deafness, jaundice, and so forth. History also records the presence of malingering in civil life. It is known that in the early days of Greece, the simulation of disease was punishable by exposure to public shame. Galen in his work referred to many acts of malingering occurring in civil life. Ambroise Paré in the sixteenth century was

struck with the common occurrence of impostors about Paris attempting to gain a livelihood by feigning disease. The methods of the malingerer have varied from one age to another. The malingerer has always been alert to the progress of science and has turned his knowledge of this progress to his own good. In military life, malingerers tend to gather together and are a menace to the morale of the group. Usually they are encouraged in their acts by existing laws and by the lack of proper punishment.

#### DEFINITION AND USE OF TERMS

Malingering may be defined as a conscious effort to deceive, in which health or illness, ability or disability is feigned or intentionally produced, in an effort to escape responsibility. The term "malingering" has come to embrace all forms of fraud relating to matters of health. The term "simulation" is used interchangeably with the term "malingering" but the latter term is the one in common use. The term "dissimulation" is employed to mean concealment of what the subject knows to be a disease or defect. Thus a man may attempt to enter the military service by covering over or hiding some disability or illness. The term "hysteria" is used frequently in place of "malingering." However, the two terms are not at all synonymous, although the two conditions may be present in the same case.

#### ETIOLOGY AND PSYCHOLOGY OF MALINGERING

It is probably true that persons whom we consider to be normal rarely adopt the pattern of malingering in their struggle for existence. In war as in peace the malingerer presents a pattern which has certain fairly constant basic factors on which his psychologic disorder develops. There is present in the malingerer (1) some fundamental defect, such as poor heredity, faulty training or repeated frustration. To this background are added (2) certain precipitating factors, such as emotional upheavals, chronic ill health or injury. As a result of the two foregoing factors there develops (3) a defective emotional reaction, characterized by strong suggestibility, exaggeration, anxiety fear, and so forth, which leads to (4) an abnormal behavior pattern, which in certain instances is termed malingering. Fetterman\* called attention to the fact that these same fundamental defects are also present in the traumatic neuroses.

It is indeed possible that many soldiers left to their civilian activities and shielded from the sudden readjustments required by military life would never have become malingerers. On the other hand, the same



persons left in civilian life but confronted with trying and painful situations undoubtedly would also have reacted by malingering

In malingering there is always the presence of an attempt to produce a false impression regarding the existence, the nature, the intensity or the origin of an illness or disability. Numerous other factors, many of which are veiled in nature, may play a role in the development of the malingering pattern. There may be a duty to avoid, a responsibility or penalty to escape, an ambition to gratify or a wrong to revenge. There may be a fear of consequences either physical or economic. It is a fairly common observation, both in civil practice and in military life, that slightly injured persons are more prone to malingering than those who are severely injured. In some instances of malingering, the physician unknowingly encourages the imposture because of his failure to recognize its early signs.

#### OCCURRENCE OF MALINGERING IN THE MILITARY SERVICE

In military life, as is also true in civilian life, malingering is probably not encountered as frequently as is usually supposed. According to Hurst,<sup>13</sup> Good<sup>10</sup> and others, true malingering is relatively rare. Rosenberg and Lambert<sup>16</sup> in a recent report stated that in their military experience malingering is very infrequent. Naturally these statements depend on what is included under the term malingering. Certainly in the armed forces malingering is not as common as is assumed by the newly appointed medical officers. Good stated that malingering was relatively infrequent in the war of 1914-1918. Catton,<sup>4</sup> in his review of the subject, quoted Munson as stating that there was not a single instance of malingering reported in the medical history of the Civil War, in spite of more than 6,000,000 admissions to sick report. In the light of our present knowledge of malingering the statement attributed to Munson seems incredible. According to Brussel and Hitch,<sup>3</sup> in the present war from 2 to 7 per cent of all patients referred to the neuropsychiatric service of military hospitals in this country are diagnosed as malingerers. Too frequently the medical officer considers every soldier who has a subjective complaint that cannot be explained readily on an organic basis as an imposter or malingerer. The "goldbricks," the fakers, the "queer sticks" are classed hastily as malingerers, when in reality many of these persons, because of some organic disease or mental handicap, merely tend to exaggerate their complaints and should be classed as pseudomalingerers. They offer a very different problem from that of the true malingerer. Unfortunately, the term "pseudomalingerer" is not satisfactory but as yet no good term has been adopted in its place.

In military life a somewhat excusable form of malingering—dissimulation—is met with in the person who simulates health or conceals a physical defect in an effort to enter the service or to obtain promotion. Many interesting stories are told of men concealing defects to get into the army. Draftees will memorize the letters on test charts, as has been related of Quentin Roosevelt in the war of 1914-1918. An epileptic patient will forget suddenly about his attacks of unconsciousness. Although the dissimulator may succeed in concealing his defect at examination, it is likely to show itself later. Hulett<sup>12</sup> stated that *"Epidemics of concealed ill health break out whenever army groups prepare to travel, as seasoned soldiers fear nothing more than separation from their comrades"*

Malingering is encountered most commonly among those who are attempting to avoid military service. Thus the draftee may allege illness, produce factitious lesions or even perform mayhem. He may feign disability by the use of drugs, he may place sugar in his urine, blood in his sputum and so forth. Many a humorous tale has been told at the expense of the draftees who have attempted to evade military service. One story attributed to Dr. Morris Fishbein deals with the draftee who obtained a 4F rating because of a hernia for which he wore a truss. His pal thought he would try the truss, since he too preferred the home front. When he returned from his examination he was asked, "What luck?" He replied that he had been put in class NE, which meant Near East—he had worn the truss upside down.

Once in the service the purpose of the malingerer is to escape unpleasant duties, to avoid transfer to other stations or to gain admittance to a hospital. It is well recognized that once the malingerer gains admittance to a hospital it is exceedingly difficult to dislodge him. The question of discharge from the army and a resulting pension is an ever-present incentive for the malingerer.

#### CLASSIFICATION

Malingers may be classified under two general headings: (1) true malingers—those who willfully claim disease or disability without evidence of organic disease, (2) pseudomalingers—those who tend to exaggerate the effects of existing organic disease or of functional disability. Under this heading are included many "gold bricks," shamers, 'scrimshakers,' men 'swinging the lead,' and so forth.

The mental patterns observed among malingers vary markedly and at times may include hysterical reactions, psychopathic tendencies, a mental defective state and even psychotic reactions, conditions which play an important role in the symptoms of the affected person.

Many writers on the subject of malingering have made classifications to meet their own fancy. Thus Gill<sup>9</sup> mentioned three types of malingering: pure malingering, partial malingering and false imputation. "Selective Service Regulations"<sup>17</sup> also mentions three groups: real malingerers, psychoneurotics and confirmed psychoneurotics. This later classification is not a classification of malingering but a mixture of terms that permits the discharge of a true malingerer on the diagnosis of psychoneurosis.

#### DISEASES AND CONDITIONS MOST COMMONLY SIMULATED

The activities of the malingerer cover the entire field of medicine. No specialty escapes his attempt at fraud. The malingerer is especially prone to complain of subjective disturbances, since they are most easily feigned and least easily detected. Among the more common complaints of the malingerer are headaches, backaches, neuralgia, exhaustion states, complaints all of which represent or have a certain negative tone and are exceedingly difficult to disprove. Another condition frequently simulated by the malingerer is motor paralysis, including disorders of gait. Sensory disturbances, visual disorders or hearing difficulties are also fields of activity for the malingerer. The malingerer may also attempt to simulate disease with reference to the heart, lungs, gastro-intestinal system or genito-urinary system, and finally he may attempt to feign insanity. These various forms of simulation are not confined to military life but also occur in civilian practice. Even if the symptoms of which the malingerer complains are confined to some medical specialty not primarily referable to the nervous system, the neuropsychiatrist should examine the subject, but only in conjunction with the specialist in whose field the symptoms complained of seem logically to fall.

#### DIAGNOSIS

To establish the diagnosis of malingering is no easy task. As pointed out by Gray,<sup>11</sup> the diagnosis can be made only after a painstaking examination and by demonstrating positive proof of fraud. The "Thespian" has given a great deal of thought to the various malingering tests and has prepared himself to cope with the examining physician. It is common knowledge that one malingerer tends to educate another and few tricks escape their Machiavellian art, especially in military service, where men are closely associated.

Malingering does not represent a specific disease entity and there is no single symptom that is pathognomonic of the condition. The signs and symptoms will vary with the individual subject and with the con-

dition that the subject attempts to simulate. It is true that malingerers taken as a group do have certain features in common which will aid the physician in his efforts at diagnosis. The fact that the subject impresses the physician as having an appearance of deceit and the actions of a guilty man does not indicate necessarily that he is a malingerer. Too frequently a subject is misjudged, his pain is belittled and his complaints are frowned upon, when in truth he has an organic disease as the basis for his trouble and for his belligerent attitude. Probably many of the former "railway spines" did represent organic disease and not malingering. Undoubtedly, an injustice was meted out in the treatment of some of these persons. Even now because of our ignorance are we unjustly accusing a person of malingering because we fail to recognize an organic cause which may exist? It is not always easy to determine whether one is dealing with a malingerer or with a "neurotic" or a hysterical person. Experience in civil life with "traumatic neurosis," "compensation neurosis" and the malingerer attests to this difficulty.

Usually the malingerer is malicious and his fraud is perpetrated consciously. The hysterical person develops his pattern unconsciously being unaware of what he is doing but the examiner may confuse it easily with the act of malingering. Because of the difficulty of making a positive diagnosis of malingering, soldiers frequently are discharged from the service with a diagnosis of psychoneurosis or, as Brussel<sup>2</sup> stated, the soldier should be discharged on the basis of "certain traits of character that render him unfit for military duty." It may be appreciated from these statements that the figures regarding the rate of discharge of malingerers from the service are not entirely accurate.

**The Examination—A GENERAL CONSIDERATIONS**—In the examination of the supposed malingerer several important points should be mentioned before the more specific examinations are discussed. First of all is to be considered the attitude of the physician in respect to the subject. The physician should have an open mind in dealing with the problem of malingering. There should be a sense of sympathy, not of hostility, on the part of the examiner. The history and examination should be detailed and accurate; they should never be hurried. Time is always on the side of the examiner. Permitted ample time, the malingerer becomes irked and even confused and frequently may trap himself. Finally, it may be necessary to outwit the subject by taking advantage of his inherent deficiencies.

Next is to be considered the attitude of the subject. The deportment of the malingerer is usually reserved and he tends to be evasive and on the defense. His conduct gives the impression of deceit. This impression may result in snap judgment which is likely to be faulty, since

other subjects than malingerers may give a similar impression. The malingerer tends to overact his part. He is blinder than he should be. He is more paralyzed than the paralyzed and he hears less than the deaf. The subject may attempt to confuse the physician with generalities. His pains are more diffuse and more vague than bona fide pains would be, he is unable to describe their intensity with clearness and his expression and reaction belie his statements. Finally, the malingerer may have some organic condition on which he builds his added false complaints, and it becomes even more difficult to separate the true from the false. In the examination of a subject suspected of malingering the physician should ask himself certain pertinent questions (1) Is

TABLE 1—DIFFERENTIAL POINTS BETWEEN ORGANIC AND PSYCHOGENIC NEUROPSYCHIATRIC CONDITIONS

	Organic	Psychogenic
Paralysis	True	False
Atrophy	True	Disuse
Sensibility	Anatomic	Bizarre
Reflexes	Altered	Unaltered
Babinski's reflex	Present	Absent
Trophic changes	Present	Absent
Fields of vision	Altered	Bizarre
Incongruities	No	Yes
Disproportions	No	Yes

there an organic or bona fide complaint or disease? (2) If there is no organic condition, is there a fraud pure and simple? (3) Is the subject exaggerating an existing condition or disease? (4) Is there a real mental state present that may be mistaken for malingering or colored by the added malingering, such as a hysterical state, a mental defective state, a psychopathic or psychotic state?

The first consideration is to determine whether the existing condition is organic or psychogenic. Table 1 illustrates some of the more common differential points between organic and psychogenic neuropsychiatric conditions.

If it is determined that the condition is not organic, it next becomes imperative to determine whether the condition is one of malingering

or is purely a hysterical type of reaction. In Table 2 are enumerated the more common differential points between malingering and hysteria.

It must be remembered that hysteria and malingering may go hand in hand. It is a known fact that many hysterical persons are also malingerers. Also, it is true, as stated by Hurst, that a person who consciously attempts to perpetrate a fraud may come to believe in his falsehood.

**B SPECIFIC CONSIDERATIONS**—1 *Examination of Subject Who States That He Has Subjective Pains and Aches*—If the impostor would abide by his story of a headache or a pain, it would be indeed difficult to

TABLE 2—DIFFERENTIAL POINTS BETWEEN MALINGERING AND HYSTERIA

	Malingering	Hysteria
Fools whom?	Others	Self
Patterns	Constant	Inconsistent
Co-operation	Resists	Assists
Mistakes	Many	Few
Self restraint	Good	Poor
Attitude	Cold	Dramatic
Suggestibility	Marked	Variable
Reaction	Sullen	Effusive
Laws	Physical	Psychologic
Appreciation	Smart	Naïve
Simulation	Symptoms can be simulated	Symptoms usually cannot be simulated
Curability	Difficult	Early

prove or disprove his claim. The impression that a physician cannot prove the presence or absence of pain is not entirely correct, for contrary to popular lay belief pain may be appraised fairly accurately unless it is of such a minor degree that it is of no special consequence. The mere fact that a person complains of subjective symptoms does not in itself indicate the act of malingering. Psychoneurotic patients are very prone to complain of subjective symptoms and, as stated by Brussel,<sup>2</sup> when placed under rigid military routine these persons will go to pieces and exhibit anxiety states or symptoms of conversion hysteria or complain of symptoms referable to the heart, stomach and so forth.

The malingerer may be so well versed in these subjective symptoms that it is difficult to distinguish between malingering and psychoneurosis.

In the investigation of complaints of subjective pain made by a suspected malingerer the following points may give aid to the physician (1) If the subject is malingering, the facial expression may belie the complaint of pain (2) The pupils are usually dilated in the presence of real pain (3) The pulse rate is invariably accelerated from 15 to 30 beats per minute if actual pain exists, especially so when the painful area is pressed upon (4) The respirations tend to increase with pain (5) The blood pressure rises with pain (6) Pallor or flushing tends to occur with pain (7) Psychogalvanic tests may give helpful information. In cases of hysteria, because of low emotional reaction, the galvanometer shows little change. In cases of malingering in which the patient has hyperemotional reactions, stimulation produces an increased galvanic reaction (8) The symptoms of which complaint is made should be open to logical interpretation based upon disease conditions (9) The nutrition remains fairly normal in the presence of long-standing complaints in malingering (10) Morphine or scopolamine may be used as described by Cozen,<sup>5</sup> in determining the degree of pain and the accuracy of the subject's story. From these observations the physician may determine whether the physical examination bears out the patient's complaints of subjective symptoms.

2 *Examination of a Subject Who Appears to Have Motor Disturbances, Paralysis, Disorders of Gait, Tremor, and So Forth*—A malingerer rarely simulates paralysis of a single muscle. His palsy may be confined to one limb or to several limbs, especially the legs. The paralysis may be either flaccid or spastic, with or without contractures. The malingerer who is simulating severe paralysis may neglect to demonstrate sensory changes, the presence of which might well be expected. If there are both motor and sensory disturbances he may neglect to present loss of sphincteral control of bowels and bladder.

The malingerer, unless he has rehearsed his part well, may be caught "with his guard down." Thus, if he is simulating hemiplegic paralysis he will tend to drag the affected leg behind him, in place of swinging it out as in a true organic hemiplegia. If the malingerer says that he cannot raise his arm or arms above the horizontal plane he may give himself away when suddenly asked to be seated, as unthinkingly the affected limb may be extended above the horizontal. Rapid passive motion in a supposedly paralyzed limb usually will elicit marked resistance, indicating the presence of muscular strength far in excess of that indicated by the subject. Fetterman<sup>7</sup> emphasized the value of the dynamometer in the testing of muscle strength in the hands. In the

presence of supposed paralysis of one leg, *Hoover's sign* may be an aid in diagnosis. The subject is requested to lift the normal leg off the couch while the examiner places a hand under the affected leg. The malingerer will press the supposedly paralyzed leg down into the hand, whereas a patient suffering from organic hemiplegia will not do this. Other valuable tests to determine motor power have been described but too many of these tests are known to the malingerer. It behooves the examiner to evolve his own tests to meet the situation before him. A most amusing test in which feigned paralysis was "cured" by a quart of Scotch whiskey, is ascribed to Foster Kennedy.

Malingers frequently complain of tremors, *tics* and muscle spasm. Close observation of the subject and repeated examinations may be necessary before a positive diagnosis is established. Disturbances of gait, including ataxia, are interesting conditions observed among malingerers. In testing the gait or station of a suspected malingerer it is important to distract the subject's attention.

A very satisfactory test employed by Freund and Sach to determine the subject's power of balance is as follows: Place the subject's feet together and have him touch his nose and then an ear, first with the right hand and then with the left hand, while his eyes are open. Now have him close his eyes and repeat the foregoing motions. If he does not sway at once, his Rombergism is probably simulated. Another test for station is *Schuster's test*. Have the patient in Romberg position with the eyes open, then with one eye closed. While he is in this position, test the pupillary reflex in the open eye. If there is a true Romberg sign, the patient should sway at once. Jones and Llewellyn<sup>14</sup> referred to the foregoing two tests and cited many more for the various muscular functions. As a rule, the simpler the test, the more satisfactory from the standpoint of the examiner.

3 *Examination of Patients Who State That They Have Sensory Disturbances*—The malingerer simulates the loss of painful sensations more frequently than the loss of tactile sensibility. The patience and ingenuity of the physician will be taxed to the limit in his examination of subjects presenting sensory changes. A few simple helpful tests follow, which are worthy of trial in the examination of patients presenting disturbances of sensation and suspected of malingering.

a. *Janet test*—Janet's yes-and no test is so simple that the malingerer fails to be alert to its significance. The subject is asked to say "no" when touched with a cotton wisp. Naturally when in an anesthetic area he should make no response, he should not say "no."

b. *Faradic test*—The use of the faradic current applied



posed anesthetic area may be of great help. The hysterical subject may allow himself to be shocked severely without apparently feeling any discomfort. The malingerer will invariably react to the painful current, thus uncovering his attempt to deceive.

c *Vibration and stereognostic tests*—As a rule, the malingerer is unfamiliar with the tuning fork and will betray himself in an attempt to impress the examiner that he cannot feel the vibrations when in truth he should. Fetterman<sup>7</sup> has recently emphasized the importance of the vibration test in the evaluation of simulated painful areas on the body.

The malingerer who is attempting to simulate an anesthetic hand is not always aware of the fact that he should be able to recognize objects placed in the affected hand. He may not know that vibration sensibility can be intact though the skin be totally analgesic. It is well for the examiner to keep an accurate record of the sensory examinations of the subject, for the records are likely to show such striking changes from time to time that they may serve as valuable proof of fraud.

4 *Examination of Patients Who State That They Have Disorders of Vision*—The physician should not attempt complicated visual tests unless he is competent in their execution. Wetzel,<sup>20</sup> Athens,<sup>1</sup> Shelton,<sup>18</sup> and others have outlined tests for visual malingering. As stated by Shelton, "the examination of the malingerer becomes a battle of wits and he may make you feel that your years of special training were spent in a kindergarten." The neuropsychiatrist should be familiar with a few simple tests concerning disorders of vision but, if added study is indicated, the subject should be examined by an ophthalmologist, who has at his disposal accurate methods of detecting visual malingering.

The malingerer who feigns blindness is likely to present himself for examination wearing dark glasses. He may be led into the presence of the examiner but close observation may reveal that he leads his escort away. To simulate total blindness is very difficult. In cases of total blindness the pupillary responses are absent. These responses cannot be affected by the subject. The blind man's fixed "listening" stare is hard to imitate. A blind person, when asked to look at his hand, will not hesitate to do so, the malingerer is likely to look away. Also, a blind person, when asked to touch his forefingers, will do so while the malingerer fails in an awkward effort. The malingerer is more likely to simulate partial blindness in one or both eyes than total blindness. Hysterical blindness, that convenient curtain that shuts out unpleasant experiences from visual memory, can usually be distinguished from

malingerer by special tests, by close observation of the subject and by the presence of other signs indicative of hysteria.

5 *Examination of Subjects Who State That They Have Defects of Hearing*—As stated by Pitman,<sup>13</sup> most persons who simulate deafness state that the deafness is unilateral. Total bilateral deafness is very difficult to simulate. The examiner should be familiar with a few simple tests relating to hearing. Thus, Weber's law refers to the fact that when a vibrating fork is placed against the skull it can be heard best in the ear that is plugged with a finger. On this basis, when a subject professes to be deaf in the right ear, if the examiner will place his finger in the subject's left ear and then hold the tuning fork against the skull behind the right ear and ask the subject if he hears it, the subject may say that he does not and at once expose himself in his fraud. If the presenting complaint of the subject has reference to hearing, the aid of an otologist should be secured at once, for if the examiner does not have proper equipment and experience in its use the malingerer may outwit him.

6 *Examination of Subjects Who Appear to Have Disorders of Phonation*—Aphonia, although comparatively easy to simulate, is stated by Jones and Llewellyn<sup>14</sup> to have been rather rare in the war of 1914-1918. The presence of organic aphonia should be easy to exclude by thorough local examination of the mouth and larynx and by a neurologic examination. It is by no means easy to distinguish hysterical aphonia from malingerer. In hysteria the onset of the aphonia is usually rather sudden and it is invariably associated with emotional upheaval. Other signs of hysteria are also usually present, such as anesthesia of the pharynx, absence of palatal reflex, and zones of anesthesia over the body. In malingerer there is an absence of organic findings and in the examination one may uncover some motive for the simulation. A rapid cure by faradic or galvanic stimulation is rather suggestive of a hysterical form of reaction. It must be kept in mind, however, that if the subject is very nervous painful electrical stimuli may bring about a so-called cure even in a case of malingerer and the electrical reactions therefore cannot be taken as positive evidence as to the underlying cause.

7 *Examination of a Subject Who Has Suspected Self-inflicted Wounds or Factitious Cutaneous Lesions*—Self-inflicted wounds are stated to be of relatively uncommon occurrence in civil life and when encountered are usually ascribed to a hysterical state. It is **probable** that serious auto mutilation is not as common in civil as in military life but if one includes the great many cases

dermatitis that are encountered in a dermatologic clinic in civil practice, the difference is not so striking as it seems at first sight

In military life the usual motives of self-inflicted wounds are to escape service, to secure hospital care, to obtain discharge from military duty or to gain compensation or pension. Self-inflicted injuries to the hands or feet are among the more common lesions that are encountered in military life. Thus injuries to the thumb or to the trigger finger are especially common. In the diagnosis of self-inflicted wounds or factitial lesions care must be exercised in not being caught unawares by the malingerer. He may well await an opportunity when many casualties are occurring to simulate in some way the lesions he sees on his fellow soldiers. Flicker<sup>8</sup> stated that in the war of 1914-1918 veritable epidemics of self-inflicted injuries occurred in an effort to escape duty or obtain a long rest.

A few facts should be kept in mind in dealing with the malingerer who inflicts injuries on himself. Frequently the subject has given more thought to the production of his lesion than to the rehearsing of his tale of woe. His story lacks conviction and variations and loopholes are obvious. The subject will usually produce lesions on exposed surfaces that he can see and usually, if he is right handed, the lesions are on the left side of the body. As a rule the lesions are in clusters and frequently smaller similar lesions are found elsewhere, suggesting recent attempts at producing newer and similar lesions. At times it may be necessary to hospitalize these persons for very close scrutiny.

The term "mayhem" is used to indicate the act of injuries a part of the body to render the subject less able to fight, thus it is mayhem to cut off a thumb but it is not mayhem to cut off an ear. Mayhem constitutes a serious military offence. While mayhem may be performed by the malingerer it may also be the act of a hysterical, mentally defective or psychotic person.

8 *Examination of Subjects Who Appear to Have Convulsions or Attacks of Unconsciousness*—An old trick of the malingerer is to feign a convulsive seizure or "an epileptic fit" as a means of escaping military duty or to gain discharge from military service. Epilepsy is claimed frequently as a defense in a criminal act, since the subject—soldier or civilian—is aware that during a period of amnesia a crime might be committed without a full realization of the act. Complaints of attacks of unconsciousness not necessarily simulating epilepsy are also offered by the recruit or soldier to gain a medical hearing.

When the examiner is confronted with the problem of convulsions or attacks of unconsciousness it is important to determine whether the symptoms represent an organic or a psychogenic condition. It may be

necessary to insist upon a period of observation in a hospital to determine the nature of the attack. Today with the employment of the electrocardiogram and the electro-encephalogram and with our added knowledge of changes of blood pressure, concentration of sugar in the blood, and so forth, the diagnosis of convulsions or attacks of unconsciousness is made considerably easier than it was formerly

The more common organic states to be kept in mind under this general heading are the following grand mal, petit mal, epileptic equivalents, jacksonian epilepsy, certain cardiac conditions, such as paroxys-

TABLE 3—DIFFERENCES BETWEEN TRUE AND FEIGNED INSANITY

	True Insanity	Malingering
History	Previous episodes	Usually no previous episodes
Onset	Usually insidious	Acute
Mental	Declares himself sane	Wishes to be declared insane
Appearance	Appears better than he is	Appears worse than he is
Conversation	Incoherent	Desultory
Actions	Consistent	Inconsistent
Convictions	<i>Very strong</i>	<i>Tends to change mind</i>
Behavior	More insane in action than in speech	More insane in speech than in action
Beliefs	Reticent	Tends to push his delusions
Coin test	Names coins correctly	Names coins incorrectly
Sleep	Can go without sleep	Cannot remain sleepless
Food	Persistent refusal	Eats, refuses tube
Pain	Suffers	Does not suffer

mal tachycardia, carotid sinus syncope postural or orthostatic syncope and heart block, and finally attacks of hypoglycemia and uremic convulsions.

Frequently it is claimed that convulsions or attacks of unconsciousness have resulted from some trauma that is connected with occupation or service. In these cases it is important to obtain an accurate history of the exact sequence of events. Frequently a diagnosis can be rendered on these facts alone although a period of observation may be required and it may be necessary for the physician or assistant to observe the subject in one of his

9 *Feigned Insanity*—Feigned insanity is not at all common but it is a condition that must be considered both in civilian and in military life. A claim of insanity is made most commonly in a criminal case and frequently the claim of insanity is not made until a charge is brought against the person. It is therefore exceedingly important to obtain an exact history including the conduct of the subject prior to the crime. Insanity rarely begins suddenly unless previous episodes of a similar character have been present. Table 3 gives the main points of difference between true insanity and feigned insanity.

Usually the insane person declares himself to be sane. He is consistent and his convictions are exceedingly strong. He is guarded and inclined to be reticent about beliefs and disbeliefs. He attempts to cover his suspicions. He will name coins or objects promptly and correctly. He may be inclined to be depressed in the morning, he may go for long periods without sleep or food, his physical health suffers and his delusions tend to progress step by step. The malingerer, on the other hand, wishes to be declared insane and he is therefore inconsistent, frequently changing his mind. He appears worse than he is. He is more insane in his speech than in his actions. He is a clumsy actor. He will name coins and objects incorrectly. He does not permit himself to be tubed or go hungry for long. He cannot remain sleepless indefinitely. He tends to harp on one or two delusions, maintains an attitude of watchfulness, and instead of being depressed at a particular period of the day, he gives the impression of being depressed all the time. As a rule the malingerer cannot continue his deception very long. If the mental derangement persists over a protracted period, the examiner must be certain that he is not dealing with a hysterical reaction, especially if the possibility of a true psychosis has been excluded.

#### TREATMENT

In the treatment of the malingerer it is very difficult to set down any rules which will cover all cases. In civil practice the problem is usually of a medicolegal nature. Prophylaxis is probably the most important single point from a military standpoint. The more carefully the entrant's examination into the army is carried out, the fewer the cases of malingering that will occur. It is common knowledge that a hastily organized regiment will have many more cases of malingering than a carefully organized regiment. In England, and recently in this country, an effort has been made to obtain a physical and mental health record of every person of military age. This record is attached to the subject's school record and accompanies him to the induction center, where it

aids materially in a more accurate estimation of the man's ability for military service

In time of war the hope of reforming the military malingerer is so remote that unless there are extenuating circumstances the man should be separated from active service as speedily as possible. At times disciplinary measures are necessary in a case of true malingering. Frequently malingerers are discharged from military service with the diagnosis of psychoneurosis, thus avoiding the necessity of court martial procedure. Again it may be advisable to discharge a malingerer on the ground of "certain traits of character that make him unfit for military duty." The question of treatment should be divided as regards true malingering and partial malingering. Frequently, prompt and strenuous therapeutic measures will prevent the development of true malingering. In cases of partial malingering in which there may be a hysterical background with features of malingering, disciplinary measures with prompt and strenuous therapeutic measures may bring about a fairly satisfactory readjustment and the soldier may be able to return to service. As stated by Brussel and Hitch,<sup>3</sup> the problem in dealing with the military malingerer is to keep him out of the service, and if he does get in—get him out.

#### COMMENT

In this discussion I have reviewed the more important neuropsychiatric aspects of malingering. It must be apparent that physicians, whether in civil practice or in military service, should be trained to detect malingering. The physician in general practice should also learn to seek aid from the neuropsychiatrist and from other physicians especially qualified to carry out detailed examinations in specialized fields. Once the diagnosis of malingering has been made, the physician should know what disposition or treatment is best suited in each individual case.

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## SLEEP PARALYSIS

J G RUSHTON

SLEEP paralysis is a term introduced by Wilson<sup>11</sup> to describe a transient, benign paralysis at the beginning or end of sleep and usually associated with a clear consciousness. The condition has been described under various names such as "night palsy,"<sup>7</sup> "delayed psychomotor awakening,"<sup>9</sup> "cataplexy of awakening"<sup>3</sup> and "predormital and post-dormital paralysis."<sup>14</sup> It is a fairly common complaint in the narcolepsy-cataplexy syndrome but seldom is reported as a separate entity. It deserves recognition and evaluation because it may cause patients distress by suggesting to them some serious condition such as epilepsy.

The paralysis always occurs during the transition between wakefulness and sleep or vice versa. It is usually a complete paralysis, though rarely the ability to open the eyes or to speak may be retained. The paralysis is flaccid but the patient in stating his complaint may say that he feels "stiff." The usual duration of an attack is a few seconds or minutes but I have seen one patient who remained in this state for two and a half hours.<sup>10</sup> During the attack the patient is fully conscious and painfully aware of his helpless condition. Even though he may have experienced previous attacks and may realize that he will recover soon from this one, he usually cannot suppress a feeling of great fear. This fear often gives rise to respirations so altered as to warn those about the patient that something is amiss. Recovery may be spontaneous or induced. If the latter, it is always by bodily contact. At times vigorous shaking is needed but often a light touch is sufficient to dispel the attack within a few seconds. Strangely enough a loud noise or the sudden turning on of lights, which so often terminates normal sleep, is quite ineffective in dispelling sleep paralysis. The frequency of attacks may vary from several times a week to once in six months or more.

Some of the outstanding features of this condition are illustrated the following two cases.

### REPORT OF CASES

CASE I.—A man, aged twenty seven years, was referred to the Clinic of respiratory distress for the past two months and roentgenogram of a mass in the thorax. As a result of various studies a diagnosis of tumor was made.

In addition to this major complaint the patient mentioned in which he feared might be epilepsy. At the age of sixteen years he



isolated grand mal convulsion This occurred while he was at work during the day One year later he began having episodes of paralysis associated with sleep These had occurred at intervals as short as two days and never longer than two months They were always associated with the process of going to sleep or awakening The patient usually had them while in bed at night but had experienced them also during the day On one occasion while sitting in a bus he became sleepy and, as he dozed off, had a typical attack from which he recovered spontaneously The paralysis was usually complete, though at times he could open his eyes At such times he considered his vision normal The patient was never able to speak during an attack but could make a grunting noise, which might attract the attention of those about him During an attack he always had considerable fear and a panicky desire to move These passed off with the paralysis Recovery was often spontaneous but, if some one would merely touch him, the paralysis promptly disappeared An interesting feature was that the termination of an attack, whether spontaneous or induced, was always preceded by a sudden, split-second "blackout" (loss of consciousness)

The patient estimated the attacks as lasting about one minute On recovery it was necessary for him to get up and walk about, for, if he did not move, a second attack would occur Until he became aware of this he had as many as six or eight attacks in succession In an effort to abort these attacks he had tried sleeping on the edge of the bed, intending to roll off and terminate the spell Unfortunately he could never summon enough strength to accomplish this maneuver The patient's father had had an isolated attack of sleep paralysis at the age of twenty-eight years The patient's only sibling had had epilepsy for the past ten years

The results of physical examination were not noteworthy except for an enlarged node in the neck The neurologic examination gave objectively negative results A roentgenogram of the thorax revealed widening of the mediastinum due to enlarged nodes A roentgenogram of the skull did not reveal anything abnormal The routine laboratory tests gave negative results The electro-encephalogram was essentially normal

CASE II—A man, aged twenty-seven years, came to the Clinic because of spells of suffocation, faintness, palpitations and sweating These had bothered him for about eighteen months and were thought to be manifestations of an anxiety tension state These spells caused him to feel profoundly weak but were not associated with paralysis, unconsciousness or convulsions In addition he had experienced attacks of sleep paralysis for six years before coming to the Clinic These would occur once or twice a week either on going to sleep or on awakening The patient estimated the duration of an attack to be a "few minutes" During this brief period he would be completely paralyzed He remained conscious throughout the attack Recovery had always been spontaneous and he did not have any knowledge of the effect of being touched by another person during an attack He had always been reluctant to discuss these spells, fearing they were epileptic He distinguished sharply between the spells of sleep paralysis and the anxiety attacks described previously The family history was negative for any similar sleep disturbance

The results of physical examination were not remarkable The neurologic examination gave objectively negative results The results of routine laboratory

tests were negative or normal. Roentgenograms of the skull and thorax did not reveal anything abnormal. The electro-encephalogram was normal.

#### COMMENT

The nature of normal sleep being poorly understood, it can be anticipated that an adequate understanding of sleep paralysis will be difficult. However, some attempt to understand it should be made. The condition may occur at any age and persist for years. One woman examined at the age of sixty-nine years had had the attacks since childhood.<sup>6</sup> The sexes are affected in about equal proportions. Sleep paralysis is probably a fairly common condition but the infrequency with which it is reported or discussed makes it seem rare. The family history is usually negative for sleep paralysis. An exception is the case of a woman who had sleep paralysis and whose aunt probably had the same malady.<sup>10</sup>

Wilson<sup>11</sup> and Lhermitte and Dupont<sup>5</sup> expressed the opinion that sleep paralysis is a nonpathologic variation of a physiologic process. Some patients who have Parkinson's syndrome may note marked alleviation of their rigidity for a short time after awakening. Thus, one patient, if he chanced to awaken suddenly during the night, could reach easily for a handkerchief beneath his pillow, a performance that a little while later became slow and laborious.

Superficially, sleep paralysis and sleep walking seem to be opposites. In the former the body seems asleep while the mind is awake, whereas in the latter the circumstances are reversed. That some definite relation may exist is suggested by one of Gowers'<sup>2</sup> patients who in his earlier years had attacks of sleep paralysis, which were replaced later by episodes of sleep walking.

Two hypotheses of sleep offer possible explanations of sleep paralysis. That of Kleitman<sup>3</sup> may be stated briefly as follows: Muscular fatigue → relaxation → sleep. If the loss of consciousness characteristic of sleep did not follow closely after muscular relaxation, sleep paralysis might be the result. On awakening, the too early return of consciousness without the resumption of normal muscular tone would have the same effect. Pavlov's<sup>4</sup> hypothesis of internal inhibition assumes that an inhibitory process spreads evenly over the hemispheres and results in sleep. If the inhibition were to reach the cerebral structures controlling motor activity at a significant interval before involving the rest of the spheres, sleep paralysis might result. Paralysis on awakening due to a reversal of this process.

Since it is not established that sleep paralysis is a variant physiologic process, other relations deserve consideration. The

ture of the complaint may suggest that it is a manifestation of a psychoneurosis Pfister<sup>9</sup> observed that all his patients having sleep paralysis had also epilepsy or a psychopathic or neuropathic taint. Persons who have an anxiety tension state may note, on going to sleep or awakening, a profound sense of weakness but it never becomes a true paralysis. In addition their symptoms are not relieved by such simple measures as terminate an attack of sleep paralysis. The hysterical trance is much more dramatic than sleep paralysis, usually persists longer and is not dissipated by simply touching the patient. The fact that sleep paralysis is a common symptom in the narcolepsy-cataplexy syndrome suggests an intimate relation between the two. Cases in which sleep paralysis existed for some time before the development of the narcolepsy-cataplexy syndrome have been noted by Levin<sup>4</sup> and by Daniels<sup>1</sup>. The latter mentioned that a cataplectic attack may be aborted or relieved by a "brisk nudge". On the other hand, the long duration of the complaint in the case reported by Lichtenstein and Rosenblum<sup>6</sup> suggests that sleep paralysis may exist as an independent condition.

Is sleep paralysis a part of, or related to, epilepsy? The observation of Pfister noted previously implies a possible relation. In the first case reported herein the patient had had one convulsion and a sibling was said to have epilepsy. Wilson in discussing the relation between narcolepsy and epilepsy stated, "The resemblances are greater than the differences". From a practical standpoint, sleep paralysis is not commonly associated with the usual manifestations of epilepsy. The electro-encephalograms of four of the patients suffering from sleep paralysis that I have seen have been normal.

The patient should be reassured that his complaint is benign. It is probably wisest to assure the patient that his spells do not represent epilepsy and disregard the somewhat academic considerations to the contrary. Beyond this reassurance there is no treatment for the condition.

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## TORULA INFECTION

WILLIAM S. TINNEY AND HERBERT W. SCHMIDT

TORULA infection is caused by a yeastlike fungus belonging to the group of fungi imperfecti. It is a rare disease with predilection for the central nervous system and the lungs. Prior to Stoddard and Cutler's<sup>9</sup> report, torulosis was not clearly distinguished from blastomycosis. Their monograph helped to clarify the classification of the pathogenic yeasts and the infections produced by them. They suggest that the organism be called *Torula histolytica* because the histolytic action is such a striking characteristic in the early lesions. Stoddard and Cutler also distinguished torulosis from other mycotic diseases, such as blastomycosis, oidiomycosis and coccidioidal granuloma. The organism causing torulosis is characterized by the absence of mycelia, absence of spore formation, presence of a capsule, reproduction by budding and the fact that there is little tendency to ferment sugars. Recently, the term "*Debaryomyces neoformans*" has been used by bacteriologists to supplant *Torula histolytica*.

The most recent comprehensive review of the subject was made by Reeves, Butt and Hammack,<sup>6</sup> who reported six cases and brought the total reported in the literature to seventy-nine cases. Among the cases reported to date, the central nervous system is involved much more frequently than the abdominal or thoracic viscera and the lungs are more often the site of infection than any other viscus. In one of Stoddard and Cutler's cases pulmonary changes were extensive. In Bettin's case<sup>2</sup> a lung abscess was present without any marked zone of inflammatory reaction around the lesion. Sheppe<sup>7</sup> was able to obtain the organism from a region of bronchopneumonia in his case. According to Sheppe, the focus of infection in the spleen, liver and kidneys, which are involved less frequently than the lungs, is always small. He found that the pulmonary lesions are usually extensive and definite cellular reaction was present. The patient studied by Berghausen<sup>1</sup> had mottled infiltration of the parenchyma of the lungs, but the organism was not isolated from the lungs. A case of acute miliary torulosis of the lungs has been reported by Hirsch and Coleman.<sup>3</sup>

### PATHOLOGY

Macroscopically, the lesions caused by torula closely simulate those of tuberculosis. Nodules composed of giant cells with central caseation are formed. There is no collection of polymorphonuclear leukocytes

One of the characteristic features of the lesions is a clear zone around the organism, composed of gelatinous material. These features are different from those of the lesions formed by blastomycosis in which polymorphonuclear infiltration is present and soluble tissue is not.

In the nervous system, the lesions localize in the meninges and in the perivascular spaces and extend into the brain substance.

The frequency with which torula meningitis and Hodgkin's disease are associated is an important and unexplained feature. Wade and Stevenson<sup>10</sup> observed coincidental lymphoblastoma in four cases and Mallory,<sup>4</sup> in five cases. The lymphoblastoma was of the Hodgkin's type in seven of these nine cases. Warvi and Rawson<sup>11</sup> have reported the eighth case of associated Hodgkin's disease and torula meningitis. Although the coincidence is not as close as that of tuberculosis and Hodgkin's disease, Mallory was of the opinion that it is too striking to be merely a matter of chance.

#### CLINICAL FEATURES

There is a difference of opinion as to the portal of entry. However, most authorities agree that the respiratory tract is the route by which the organisms enter the body. Because of the frequently insidious onset and the protean manifestations of torulosis, the clinical diagnosis may be extremely difficult. In the majority of cases the earliest and most prominent symptoms are referable to the central nervous system. The patient usually complains of severe, persistent headache associated with vomiting. Stiffness of the neck with positive Kernig and Brudzinski signs is frequently found. Vertigo, visual disturbances and hemiplegia are not uncommon. The symptoms of increased intracranial pressure are not associated with any localizing features. A diagnosis of brain tumor, brain abscess, encephalitis or meningitis is often made. Mental symptoms are occasionally so prominent that the patient is committed to a mental hospital because of an erroneous diagnosis of psychosis. Not infrequently the temperature and leukocyte count are normal and the patient does not appear acutely ill.

When a pulmonary lesion is present, the clinical findings may suggest tuberculosis, lung abscess, bronchiogenic carcinoma or even syphilis of the lung. The site of infection in the lungs is characteristically in the lower lobes. This fact, in addition to a negative sputum for *Mycobacterium tuberculosis*, may lead to the correct diagnosis. In some cases it is possible to isolate the organism from the sputum.

The correct antemortem diagnosis can be usually established as the result of a diligent search of the cerebral spinal fluid for the organisms. Stiles and Curtiss<sup>3</sup> have studied the changes in the cerebrospinal fluid

and their findings may be summarized briefly as follows. The total number of cells was less than 600 per cubic millimeter in every case studied except one. The majority of cells were lymphocytes. The pressure was increased in most instances, but only exceptionally was it more than 450 mm. Values for protein were usually more than 40 mg per 100 cc of cerebrospinal fluid. In the majority of cases determinations of sugar revealed less than 40 mg per 100 cc of cerebrospinal fluid. Values for chloride ranged between 460 and 760 mg per 100 cc of cerebrospinal fluid. Individual gold curves varied considerably. The differential count of cells in the spinal fluid occasionally revealed that 55 per cent of the cells were polymorphonuclear leukocytes.

#### REPORT OF CASES

**CASE I**—A man, aged thirty-two years, a native of Wisconsin, was brought to the Clinic January 11, 1942, in coma that had persisted for six days. He had been well until December 27, 1941, when a constant severe right frontotemporal headache developed. The headache persisted and on December 31, 1941, he vomited several times. Lumbar puncture was performed elsewhere and the cerebrospinal fluid pressure was found to be 22 cm of water. On January 2, 1942, another lumbar puncture was done and the pressure was 29 cm of water. The cerebrospinal fluid was xanthochromic. The value for the sugar was 51 mg per 100 cc, for protein 158 mg per 100 cc, and for chlorides 660 mg per 100 cc. On January 3, 1942, an exploratory operation of both frontal regions, done elsewhere, revealed nothing abnormal. On January 5, a stiff neck developed and the patient became stuporous. On January 6, pneumonia developed, the temperature ranged from 102° to 104° F and the pulse rate was 160 per minute. The temperature and pulse rate improved after the administration of sulfathiazole.

On examination at the Clinic the patient was found to be semistuporous and moderate stiffness of the neck and paresis of all extremities were noted. The leukocyte count averaged between 9,000 and 16,000 per cubic millimeter of blood. A roentgenogram of the thorax revealed infiltration of the right upper lobe. On January 26, 1942, a culture of the cerebrospinal fluid on dextrose agar was positive for *Debaryomyces neoformans* (*Torula histolytica*).

A diagnosis of torula meningitis was made. Sulfadiazine was administered for thirty days and the concentration of the drug in the blood was maintained at more than 5 mg per 100 cc. On February 13, 1942, the patient was given 10 cc (0.5 mg per cubic centimeter) of tyrocidine intrathecally. This dose was repeated the following day. On February 20, he received 15 cc (0.5 mg per cubic centimeter) of tyrocidine intrathecally. The patient became progressively worse and died March 8.

**Necropsy**—Aside from the central nervous system the examination was essentially negative. External examination of the brain revealed flattening of the convolutions and a rather profuse exudate around the cranial nerves at the base of the brain. Dilatation of the ventricles was caused by partial obstruction of the foramina of Luschka and Magendie by exudate at the base of the brain. There were small adhesions in the lateral ventricles but no exudate was present. The third ventricle and sella were normal, as were the mastoid and internal ear on the left.

The right middle and internal ears contained a yellow gelatinous exudate. The paranasal sinuses were clear. Examination of the spinal cord revealed a heavy yellow exudate in the dural space, particularly around the cauda equina.

*Comment*—This case of torula meningitis is an example of the difficulty so often encountered in the diagnosis of the disease. Before the diagnosis was established by obtaining a positive culture, the following tentative diagnoses were made: brain tumor, subdural hematoma, tuberculous meningitis and encephalitis. The case is also of interest because of the fulminating course of the disease and because an ante-mortem diagnosis was established.

**CASE II**—A man, twenty three years of age, a native of Nebraska, was admitted to the Clinic September 16, 1942, because of severe headache and vomiting. He had been well until June, 1938, when painless swelling of the neck developed. A diagnosis of Hodgkin's disease was made elsewhere at biopsy of a cervical node and the patient was given a course of roentgen therapy. Following this, he was asymptomatic and was inducted into the army in February 1941. In October, 1941 he noticed generalized lymphadenopathy. In November, 1941 pain in the left side of the thorax, intermittent fever and recurrent left pleural effusion developed. Biopsy of another cervical lymph node at an army hospital again revealed Hodgkin's disease. He received another course of roentgen therapy and was asymptomatic until July, 1942, when the pain in the thorax recurred and he became weak. In August 1942, headaches developed and gradually became severe. Following the onset of headaches, he had formed visual hallucinations, vomiting, diplopia and stiffness of the neck.

On examination at the Clinic the patient was found to have bilateral choking of the optic disks and retinal hemorrhages. There was a sixth nerve palsy on the right. At the base of the left side of the thorax there was flatness to percussion and diminished breath sounds. All laboratory examinations were essentially negative aside from the roentgenogram of the thorax, which showed an elevation of the left side of the diaphragm and obliteration of the left costophrenic angle. The diagnosis of Hodgkin's disease was confirmed by examination of a cervical node.

Roentgen therapy was started on September 19, 1942, but the patient became progressively worse and died September 23.

*Necropsy*—Fine nodules covered the surface of both lungs and were scattered throughout the parenchyma. Thick, fibrous adhesions covered the left lung. The left lower lobe was separated with difficulty from the diaphragm in which there were numerous nodules. The spleen weighed 376 gm. Its surface was normal, the tissue was firmer. The cut surface was fibrous. The liver weighed 1,000 gm. Scattered over the surface and throughout the substance of the liver were numerous nodules measuring 1 to 2 mm. in diameter. The right kidney weighed 100 gm. Many yellow nodules measured up to 3 mm. in diameter. The kidneys were edematous and cloudy. These changes were most marked in the cortex of the brain and along the longitudinal sinuses. There was moderate swelling of the brain and thinning and atrophy of the left substantia nigra. The cerebellum appeared normal.



On microscopic examination the thymus was found to contain a few foreign body giant cells containing torulae. All lobes of the lungs revealed patches of alveoli filled with endothelial cells and foreign body giant cells containing torulae. The spleen was extremely fibrous with hyperplasia of the reticulo-endothelial cells and also many giant cells containing torulae. In the liver the fibrous tissue and lymphocytes in the portal spaces were increased and there was one area of caseation containing giant cells and torulae. This area of caseation was surrounded by endothelial cells and lymphocytes. In the cortex and medulla of both adrenal glands many collections of torulae were surrounded by fibrosis. Both kidneys contained regions in which there were collections of torulae and giant cells. There were a few foci of lymphocytes and fibrosis. The acini of the prostate gland were filled with giant cells and torulae. The testes and thyroid gland also were filled with giant cells and torulae.

*Comment*—To our knowledge, this is the ninth case reported in which Hodgkin's disease and torulosis have been associated. Practically every organ was involved by both processes and the lesions were always closely associated. Since torulosis is usually confined to the central nervous system and in occasional cases also may involve the lungs, this is an interesting case. Such widespread visceral involvement is most unusual.

**CASE III**—A man, twenty-five years of age, a native of Louisiana, came to the Clinic March 26, 1943, because of constant headaches and vomiting. He had been well until December, 1942, when he first noticed a frontal headache which interfered with his sleep. Bending his head, stooping, coughing or sneezing made the headache much worse. The vomiting was projectile in character. Three weeks prior to admission bilateral tinnitus appeared and became constant.

Physical examination at the Clinic was essentially negative aside from slight rigidity of the neck. The roentgenogram of the thorax is shown in Figure 71. There was an inflammatory process at the left base with multiple cavitation. A lumbar puncture was performed March 31, 1943. The pressure of the cerebrospinal fluid was 9 cm of water. Determination of the sugar revealed 24 mg per 100 cc of total proteins 170 mg per 100 cc and of chlorides 676 mg per 100 cc. The lymphocyte count was 118 per cubic millimeter. Culture of the cerebrospinal fluid on hormone blood agar was positive for *Debaryomyces neoformans* (*Torula histolytica*).

Bronchoscopic examination was performed on April 19, 1943, and a small amount of mucoid secretion was aspirated from both lower lobe bronchi. Culture of this secretion on blood agar and dextrose agar was positive for *Debaryomyces neoformans* (*Torula histolytica*).

On April 13, 1943, 20 cc (0.5 mg per cubic centimeter) of tyrocidine was injected intrathecally. The same procedure was repeated the following day, with 40 cc (0.5 mg per cubic centimeter) of tyrocidine and on April 17, with 20 cc. A rather severe reaction characterized by backache, nausea and vomiting followed this treatment. The patient was given sulfathiazole, 90 grains (6 gm) a day for eight days, to maintain a concentration in the blood of more than 6 mg per 100 cc. The patient was dismissed April 28, 1943, subjectively improved and

was advised to continue the sulfathiazole therapy under the care of his family physician. In December 1943, the patient was practically asymptomatic and able to go on a hunting trip

*Comment*—The diagnosis was established in this case by culture of the cerebrospinal fluid and the bronchial secretions obtained at bronchoscopy. The multiple cavities in the base of the left lung, as shown in the roentgenogram of the thorax (Fig 71), rather closely simulated multiple cysts. Because of the results obtained by Marshall and Teed<sup>5</sup> with sulfonamide therapy, this patient was given sulfathiazole



Fig 71—Inflammatory process with multiple cavities at the base of the left lung

It is impossible to be certain that sulfathiazole was responsible for his symptomatic improvement, but we feel that the drug should be given a more trial because the treatment of *Torula* infection is unsatisfactory and with the possible exception of the sulfonamides, nothing has been found to alter the course of the disease.

#### SUMMARY

*Torula* infection is caused by a yeastlike fungus that belongs to a group of fungi imperfecti and has a predilection for the central nervous system and the lungs. The antemortem diagnosis is difficult.

cause of the protean manifestations of the disease. Three cases are reported in this paper, in two of these the antemortem diagnosis was established. In one case general involvement of the viscera and Hodgkin's disease were present.

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# PAPILLEDEMA IN OPTIC NEURITIS AND TUMOR OF THE BRAIN

ERNEST M. HAMMES, JR

PATHOLOGIC elevation of the head of the optic nerve has been designated by a variety of names, of which "choked disk," papilledema, papillitis and optic neuritis are perhaps the most common. This varied and frequently confused terminology is due to the fact that the causes of this elevation are numerous and to the fact that attempts are often made to use a specific term to designate the elevation found in each of the more common disease processes producing it. Whatever the terminology, elevation of the head of the optic nerve constitutes a valuable objective diagnostic sign.

To designate the lesion observed ophthalmoscopically, the term "papilledema" is probably the most satisfactory since it does not denote any specific causative factor. The differential diagnosis of the various underlying causes of the papilledema cannot be obtained by ophthalmoscopic examination alone. The term "choked disk" should be reserved for the papilledema associated with increased intracranial pressure, the term "optic neuritis" should be used to designate a local disturbance of inflammatory or vascular nature in the optic nerve itself, which results in a visible edema of the optic nerve.

The finding of papilledema, taken in conjunction with the history and other objective signs, narrows the list of diagnostic possibilities considerably, but all too frequently the examining physician finds himself unable to determine definitely the type of papilledema present in an individual case. This study has been undertaken in an attempt to elicit points of value in the differential diagnosis of two of the more frequently encountered types of papilledema—"choked disk" and optic neuritis.

Physiologic variants not infrequently cause an actual or apparent elevation of the head of the optic nerve and may lead to errors in diagnosis provided their occurrence is not recognized. Bedell<sup>2</sup> lists four such physiologic changes: glial excess on the disk, colloid within the disk, medullated nerve fibers at the margin of the disk, and refractive errors with distortion of the disk. Among the conditions which may produce an elevation of the head of the optic nerve are increased intracranial pressure from whatever cause, intracranial tumors, inflammation, and congenital disorders producing obstruction of the ventricular system, subarachnoid hemorrhage, mal-

tension, plumbism,<sup>5, 6</sup> blood dyscrasias,<sup>9</sup> and various local orbital and ocular disturbances of which optic neuritis is perhaps the most common and important

#### MATERIAL

This study is based on two groups of cases

**Group 1**—This group includes twenty-five cases of tumor of the brain in which choked disk was present. The cases otherwise were taken at random. In all of the cases the diagnosis was confirmed at operation or at necropsy. Twenty of these tumors were supratentorial and five infratentorial. The tumors were classified as follows: meningioma in six cases, spongioblastoma multiforme in six cases, oligodendroglioma in five cases, astrocytoma in three cases, and pinealoma, ependymoma, paraphysial cyst, neurofibroma and sarcoma in one case each.

Fifteen of the patients in this group were males and ten were females. The ages of the patients ranged from fourteen to fifty-nine years and the average age was 33.6 years.

**Group 2**—This group includes twenty-five cases of optic neuritis in which there was elevation of the head of the optic nerve. The cases otherwise were taken at random. In all of the cases the diagnosis was made by members of the Section on Ophthalmology, to whom I wish to express my appreciation. The diagnosis was based on the clinical findings and on the course of the disease. As the mortality in this condition is virtually nil, there was no opportunity for pathologic verification of the diagnosis.

Ten of the patients were males and fifteen were females. The ages of the patients ranged from twelve to fifty-nine years and the average age was 30.8 years.

Lumbar puncture was performed in fourteen of the twenty-five cases and the pressure of the cerebrospinal fluid was normal in all of these cases. The highest pressure encountered in any of the fourteen cases was 19 cm. of water. A definite cause for the optic neuritis was established in only four of the twenty-five cases. Multiple sclerosis was present in three of these cases and neuromyelitis optica was present in the remaining case. In two other cases a consultant in the Section on Neurology made a diagnosis of "probable multiple sclerosis." In another case, dental sepsis was present and it was felt that this probably was an etiologic factor. In eight of the twenty-five cases in this group, the urine was examined quantitatively for lead and arsenic. In seven of eight cases there was no evidence of either of these metals in the urine but in the remaining case a twenty-four hour specimen of urine contained 0.04 mg. of lead.

A subsequent examination was performed in seventeen of the cases in this group. In all of the seventeen cases, the symptoms improved, and at the time of the subsequent examination, the elevation of the optic disk was not as great as it had been at the time of the previous examination. In nine of the seventeen cases, the improvement amounted to subjective and objective recovery. Of the eight patients who had not recovered completely before they were dismissed from the Clinic, only two had been observed for more than two months. Follow-up data were not obtained in eight of the twenty-five cases in this group.

### SYMPTOMS

Table 1 shows the duration of the symptoms which reasonably could be attributed to the disease which caused the elevation of the head of the optic nerve. In the cases in group 1 (cases of tumor of the brain), the average duration of symptoms was much longer than it was in the

TABLE 1—DURATION OF SYMPTOMS PRIOR TO DIAGNOSIS OF PAPILLEDEMA

Underlying Disease	Duration	
	Range	Average
Tumor of brain.	3 wks. to 9 yrs.	15.2 mo.
Optic neuritis	3 da. to 6 wks.	16 da.

cases in group 2 (cases of optic neuritis). In twenty-one, or 84 per cent, of the cases in group 1, the symptoms had been present for more than six weeks before the choked disk was discovered. In every case of optic neuritis in this series the symptoms had been present less than six weeks.

Diplopia was present in twelve, or 48 per cent, of the cases of tumor of the brain and in only one, or 4 per cent, of the cases of optic neuritis. In the last mentioned case, the diplopia was fleeting and transient.

Other subjective visual symptoms occurred far more frequently in the cases of optic neuritis than they did in the cases of tumor of the brain. In twelve of the cases of tumor of the brain there were no visual symptoms whatever and in five other cases the only visual symptom was blurred vision. A progressive loss of vision had been observed in only four of the cases of tumor of the brain. In these cases, the loss of vision had occurred gradually and had been noted by the patients for two months or more before a diagnosis of choked disk was made. In

contrast, all of the patients in the cases of optic neuritis complained of definite loss of vision. In these cases visual impairment varied from a slight decrease in visual acuity to complete blindness. In all of these cases, the impairment of vision had developed rather suddenly, that is in a few days or less.

*Headache* without ocular pain occurred in twenty-three, or 92 per cent, of the cases of tumor of the brain and in only six, or 24 per cent, of the cases of optic neuritis. *Ocular pain* with or without headache was present in fourteen of the cases of optic neuritis. In five cases of optic neuritis there was no history of headache or ocular pain. Nine of the patients who had optic neuritis had ocular pain that was not associated with headache. Ocular pain unassociated with headache did not occur in any of the cases of tumor of the brain. Headache occurs more frequently in cases of tumor of the brain than it does in cases of optic neuritis. On the contrary, ocular pain occurs more frequently in cases of optic neuritis.

#### OPHTHALMOSCOPIC FINDINGS

**Unilateral Papilledema**—In twenty, or 80 per cent, of the cases of optic neuritis, the elevation of the head of the optic nerve was unilateral. In contrast, this was true in only one of the cases of tumor of the brain. In this case, the patient had a right basofrontal meningioma and there was an elevation of the head of the optic nerve on the right side. The presence of unilateral papilledema seems to favor the diagnosis of optic neuritis, however, the presence of bilateral elevation of the head of the optic nerve is of no help in the differential diagnosis of optic neuritis and tumor of the brain.

**Degree of Elevation of Head of the Optic Nerve**—The statement that an elevation of the head of the optic nerve that is greater than 2 diopters is incompatible with a diagnosis of optic neuritis occasionally is found in textbooks and in the literature. There is evidence that a low degree of papilledema is encountered more frequently in cases of optic neuritis than it is in cases of tumor of the brain. An elevation of more than 2 diopters was found in only seven, or 23 per cent, of the thirty involved eyes in the cases of optic neuritis whereas it was present in twenty-seven, or 55 per cent, of the forty-nine involved eyes in the cases of tumor of the brain. An elevation up to 5 diopters was found in an appreciable number of cases in each group, therefore, its value in the differential diagnosis was nullified. An elevation of 6 diopters or more may be considered evidence in favor of tumor of the brain.

Table 2 shows the degree of elevation of the optic disks in the two

groups of cases. The greatest degree of elevation observed in any of the cases of optic neuritis was 5 diopters. In the case in which this degree of elevation was observed, the papilledema was bilateral and the degree of elevation in the other eye was 4 diopters. Neurologic examination, which included determination of the pressure of the cerebrospinal fluid, did not disclose any abnormality. The visual acuity was so poor that the patient was able to distinguish only moving objects. Treatment consisted of the intravenous administration of typhoid vaccine. Four weeks after treatment was begun, the ocular fundi were normal and the vision in each eye was found to be 6/7. Examination of the visual fields at this time disclosed bilateral paracentral scotomata which were subsiding.

**Other Ophthalmoscopic Findings.**—Narrowing of the retinal arterioles, capillary engorgement and venous dilatation were not found to be significantly different in the two groups of cases. The same may be

TABLE 2—ELEVATION OF OPTIC DISK

	In Cases of Tumor of Brain	In Cases of Optic Neuritis
Range	N.M.E.* to 8 diopters	N.M.E.* to 5 diopters
Average	3.1 diopters	1.8 diopters
Percentage of involved eyes in which elevation was more than 2 diopters	55	23

\* No measurable elevation.

said of the frequency with which hemorrhage was found in the retina. Exudates were observed in fourteen (28 per cent) of the forty-nine involved eyes in the cases of tumor of the brain and in only one (3 per cent) of the involved eyes in the cases of optic neuritis. A partial or complete macular star was observed in four of the involved eyes in the cases of tumor of the brain but this was not observed in any of the cases of optic neuritis. At the time the patients were first examined at the Clinic pallor of the optic disk was observed in approximately 10 per cent of the involved eyes in each group of cases.

#### VISUAL ACUITY

In both groups of cases the visual acuity ranged from normal to complete loss of vision. The vision of forty-six of the forty-nine involved eyes in the cases of tumor of the brain was better than 6/30 according to Snellen's test types. This degree of visual acuity was



present in only three of the thirty involved eyes in the cases of optic neuritis

In the three eyes in the cases of tumor of the brain in which the vision was 6/30 or less, the involvement was associated with increased intracranial pressure, as disclosed roentgenologically by erosion of the floor of the sella turcica. In these three instances, it is probable that the loss of vision was due to pressure on the optic nerve. In thirty-eight of the forty-nine involved eyes, the visual acuity was normal. Vision was considered normal if it was not less than 6/7 for distance or not less than 14/21 when tested with the A M A Reading card for near vision. The vision of ten of these eyes would have been considered decreased if they had been tested only for distant vision. The importance of testing near vision as well as distant vision cannot be overemphasized. In every case of tumor of the brain in which both near vision and distant vision were decreased in an involved eye, roentgenologic examination disclosed evidence of increased intracranial pressure or ophthalmoscopic examination revealed hemorrhage into the macula or pallor of optic disk.

Only two of the thirty eyes involved in optic neuritis had normal vision. In the case of one of these eyes, the patient complained of a blind spot in the left eye, which was the one that was involved. The vision in this eye was 6/6 and that in the right eye was 6/4. When the patient recovered a month later, the vision in each eye was 6/4. It is evident that this patient had unusually acute vision. Although vision of 6/6 usually is considered normal, it actually represented in this case a decrease in visual acuity. In the other instance in which the vision of an affected eye was normal, the optic neuritis began in the left eye and later involved the right eye. When the patient first came to the Clinic, ophthalmoscopic examination disclosed bilateral papilledema of 1 diopter. At this time, the vision of the left eye was 6/60 and 14/224 and the vision of the right eye was 6/6 and 14/25. Eleven days later, it was found that the vision of the right eye was reduced to 2/60. When the patient recovered seven weeks later, the vision of each eye was normal. Papilledema that is due to optic neuritis at times may precede by a few days the functional involvement of the fibers that subserve macular vision. This probably happened in the right eye in the case that has just been mentioned.

Preservation of normal visual acuity is one of the most valuable aids in distinguishing the choked disk of tumor of the brain from papilledema that is due to optic neuritis. An elevated nerve head associated with a loss of visual acuity favors the diagnosis of optic neuritis, es-

pecially if roentgenologic examination does not disclose any evidence of increased intracranial pressure

### CHANGES IN THE VISUAL FIELDS

In all of the cases in each group of the visual fields were plotted with the perimeter and also on the Bjerrum screen. In all of the cases in which the blind spot could be measured, it was found to be enlarged. Although this finding is indicative of papilledema, it is of no help in distinguishing the various causes of papilledema. The perimetric findings are shown in Table 3.

TABLE 3—PERIMETRIC FINDINGS

Findings	Cases of Tumor of Brain		Cases of Optic Neuritis	
	Number	Per Cent	Number	Per Cent
Normal visual field*	18	72	0	0
Central scotoma	1	4	19†	76
Paracentral scotoma	0	0	1	4
Homonymous hemianopsia	3	12	0	0
Binasal contraction	1	4	0	0
Vision too poor for perimetry	2	8	5	20

\* Exclusive of enlarged blind spots.

† In one of these cases, the involvement was bilateral. The visual field of the left eye was normal but a cecocentral scotoma was present on the right side.

With the exception of enlarged blind spots, the visual fields were normal in eighteen or 72 per cent, of the twenty-five cases of tumor of the brain. Homonymous hemianopsia was present in three of the cases of tumor of the brain. In each of these cases, a tumor was situated in the opposite temporal lobe. In one case the patient had a central scotoma in the eye ipsilateral to a meningioma of the sphenoidal ridge. In these four cases, the defects in the visual fields can be assumed to have been due to direct interference with the visual pathways. In two cases, the vision was too poor to permit satisfactory examination of the visual fields, and in another case perimetry disclosed binasal contraction. In these three cases, the changes in the visual fields presumably were due to chronic papilledema and secondary optic atrophy.

Defective visual fields were observed in all of the cases of optic neuritis. In one case, in which the involvement was bilateral, the visual field of the left eye was normal but a cecocentral scotoma was present on the right side. The disease in the left eye evidently had improved as the patient had observed severe visual impairment in this eye three weeks previously. The results of examination of the visual field of the thirty involved eyes in the twenty-five cases of optic neuritis were as follows. As previously mentioned, the visual field of only one of the thirty eyes was normal. In one of the eyes, there was an altitudinal contraction at the time of the first examination but later examination disclosed a cecocentral scotoma. A central or cecocentral scotoma was found in twenty-one instances. In six of the thirty eyes, the vision was too poor to permit satisfactory study of the visual fields. Three of these six eyes were blind. In twenty-eight, or 93 per cent, of the involved eyes in the cases of optic neuritis, examination of the visual fields disclosed either a scotoma of the central field of vision or vision that was too poor to permit plotting of the visual field.

#### ROENTGENOLOGIC EXAMINATION

In eight of the twenty-five cases of tumor of the brain, roentgenologic examination of the head did not disclose any abnormality. In thirteen cases, it disclosed erosion of the sella turcica, which was due to increased intracranial pressure. In one of the thirteen cases and in four other cases, roentgenologic examination disclosed localized changes such as erosion of the skull over the tumor or calcification within the tumor. In seventeen, or 68 per cent, of the cases, there was roentgenologic evidence of an expanding intracranial lesion.

The head was examined roentgenologically in twenty-two of the twenty-five cases of optic neuritis. In nineteen of the twenty-two cases, this examination did not disclose any abnormality. In the three remaining cases, the only abnormalities were anatomic variations, such as calcification of the choroid plexus, benign frontal hyperostosis and an increase in the vascular markings in the skull. These anomalies apparently were not significant clinically.

#### COMMENT

Attempts have been made to distinguish the papilledema of increased intracranial pressure from that of optic neuritis on the basis of the presence of the physiologic cup in the former condition and its absence in the latter.<sup>1, 8</sup> Because the physiologic cup frequently cannot be seen in cases in which there is no pathologic lesion (the structurally full

disk in which the cup is filled with an excess of glia), the absence of the cup cannot be considered a reliable diagnostic sign

Of the various diagnostic factors investigated in this study, the duration of symptoms prior to the discovery of papilledema proved one of the most valuable. As previously stated, the duration of symptoms was much longer in cases of tumor of the brain than it was in the cases of optic neuritis. This most likely is due to the more acute nature of optic neuritis and to the fact that severe impairment of vision occurs early in the course of the disease and causes the patient to seek medical aid.

As a corollary, elevation of the head of the optic nerve that is discovered accidentally and is not accompanied by any ocular symptoms is more likely to be due to tumor of the brain than it is to optic neuritis.

Careful plotting of the visual field should be carried out whenever possible in all cases in which the cause of papilledema is uncertain. In cases in which examination does not disclose any measurable elevation of the head of the optic nerve, one frequently wonders whether or not papilledema actually exists. In such cases, measurement of the blind spot will prove helpful. De Schweinitz<sup>7</sup> first observed that an enlargement of the blind spot often was one of the earliest signs of an elevation of the head of the optic nerve and that it occasionally could be elicited before any definite changes were demonstrable in the ocular fundus. The finding of the various perimetric defects that already have been mentioned is an additional diagnostic aid. A rough estimation of the visual fields by the confrontation method frequently will fail to disclose a small scotoma or one of slight density. The extra time and effort required to make a careful examination of the visual fields are well spent and may obviate the necessity of a further series of time consuming tests.

Electro-encephalography was employed in fourteen of the cases of tumor of the brain. In three of the cases it did not reveal any abnormality but in the remaining eleven cases it disclosed delta localization, which subsequently was proved correct in nine of the cases. This procedure was employed in three of the cases of optic neuritis but it did not show any abnormality in any of these cases. While the number of cases in which electro-encephalography was used is too small to permit definite conclusions regarding the value of this procedure, it indicates that this test may be of value in cases in which the differential diagnosis proves difficult, especially if adequate diagnostic criteria were obtained by the use of the procedure in a large number of similar cases.

Some authors<sup>3, 4</sup> have said that the optic disk is red in cases in which papilledema is due to optic neuritis and gray or translucent in cases of

choked disk This difference in color has been considered to be of value in the differential diagnosis of these two conditions It is doubtful if these differences in color can be observed in every case or in all stages of the disease

The presence of papilledema is generally, and very properly, considered a contraindication to lumbar puncture because of the danger of cerebellar herniation and medullary compression as a result of interference with the dynamics of a cerebrospinal fluid in which the pressure is increased In an occasional case, one is left with no other recourse than to do a lumbar puncture to distinguish an elevation of the nerve head caused by increased intracranial pressure from one that is due to optic neuritis If the ocular findings and symptoms are carefully evaluated, however, the number of instances in which this is necessary can be reduced to a minimum

#### SUMMARY

Papilledema that is demonstrable ophthalmoscopically and is not associated with pallor of the optic disk is more likely to be due to increased intracranial pressure than it is to optic neuritis if one or more of the following criteria are present (1) if the symptoms have been present for more than six weeks, (2) if diplopia is present, (3) if headache is present, especially if it is not accompanied by ocular pain, (4) if there is no subjective loss of visual acuity, (5) if the degree of elevation of the head of the optic nerve is high, especially if it is more than 5 diopters, (6) if the visual acuity is better than 6/30, (7) if the visual field is normal except for an enlarged blind spot, and (8) if roentgenologic examination of the skull discloses erosion of the floor of the sella turcica On the other hand, the papilledema is more likely to be due to optic neuritis if one or more of the following criteria are present (1) if the symptoms have been present only for a short time, that is less than six weeks, (2) if the patient complains of pain or soreness in the eye, especially when the eyeball is moved, (3) if there is subjective loss of vision, (4) if the degree of elevation of the head of the optic nerve is low, that is less than 2 diopters, (5) if visual acuity is less than 6/60, (6) if a scotoma involves the central field of vision, and (7) if roentgenologic examination of the skull does not disclose any abnormality

It must be recalled that in cases in which papilledema is due to increased intracranial pressure the elevation of the head of the optic nerve frequently is less than 1 diopter and that in 45 per cent of the twenty-five cases of tumor of the brain, the elevation was 2 diopters or less It also must be remembered that in cases in which the elevation

is 4 diopters or more the papilledema eventually may be proved to be due to optic neuritis. The discovery of a perimetric defect that is indicative of involvement of an optic tract or optic radiation is conclusive evidence that the papilledema is due to increased intracranial pressure and not to optic neuritis.

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# BENIGN AND MALIGNANT MOLES (NEVI); THEIR DIFFERENTIATION AND TREATMENT

HAMILTON MONTGOMERY

I SHALL describe various types of benign and malignant nevi and the conditions with which they may be confused, and then I shall discuss their treatment. There is no uniformity of agreement regarding clinical or histopathologic classification or treatment of different types of nevi. For these questions the reader is referred to the appended list of references. I shall not describe some of the uncommon forms of nevi.

## NEVUS PIGMENTOSUS

The common or ordinary mole usually is present at birth but may develop at any time during life, most frequently before puberty. The



Fig 72—*a*, Multiple benign pigmented nevi of various sizes on the thorax, *b*, typical hairy nevus on thorax.

lesions vary greatly in size, from those scarcely visible and pinhead in size to giant moles involving extensive portions of the body, such as

the so-called bathing trunk nevus. Pigmented nevi may be solitary but tend to be multiple (Fig. 72) and occur anywhere on the body including the mucous membranes. The two most common types are, first, the small deeply pigmented flat type (junction type of Traub), which may or may not contain hairs and which occurs especially on the extremities, and secondly, the soft, smooth, slightly elevated, moderately pigmented mole containing hairs and seen especially on the face, neck, trunk, thighs, buttocks and genitalia. Moles may also be raised or pedunculated, with a smooth or furrowed or even warty (verrucous) surface. All moles are characterized histopathologically by the presence of nevus cells.

Linear nevi with or without pigment may contain nevus cells but more frequently belong in the group of epithelial nevi. When moles are multiple and of the color of the skin or have a yellowish hue, they may be confused with fibroma, cutaneous tags or even leiomyoma or xanthoma. Histopathologic distinction may be necessary. Pigmented nevi are to be distinguished from any of the nevi to be described later. However, they may occur in association with these nevi or in association with conditions such as von Recklinghausen's disease (neurofibromatosis), lipomas and various congenital anomalies. Superficial flat moles may be confused with freckles, or lentigines, which latter, however, in the beginning show merely increase of pigmentation of the skin and do not contain any nevus cells.

Whether the ordinary pigmented nevus is present at birth or begins later in life, it tends, when once developed, to remain as such without change of size or of degree of pigmentation. When such changes take place, transition to melano-epithelioma (melanocarcinoma) must be suspected.

#### VERRUCA SENILIS (SEBORRHEIC KERATOSIS)

Verruca senilis is essentially a delayed epithelial nevus characterized as a rule by multiple lesions usually developing in the latter decades of life. The lesions occur chiefly on the trunk and arms, less commonly on the neck and face (Fig. 73, *a*, *b* and *c*). The mucous membranes, palms and soles are not involved. The lesions begin as light brown, slightly elevated, tiny plaques a few millimeters in diameter which tend to increase in size up to several centimeters and become deeply pigmented until some are very deep brown or even bluish black in color. The lesions usually are covered with a thick greasy scale and have the appearance of being stuck on the skin. Dermatosis papulosa nigra occurring in Negroes apparently represents a variant of verruca senilis differing in that the lesions develop earlier in life and are seen frequently on the face. Verruca senilis is characterized histopathologically by



increase of basal cells with increased deposition of melanin pigment and a benign proliferation of basal and prickly cells. These changes are ac-

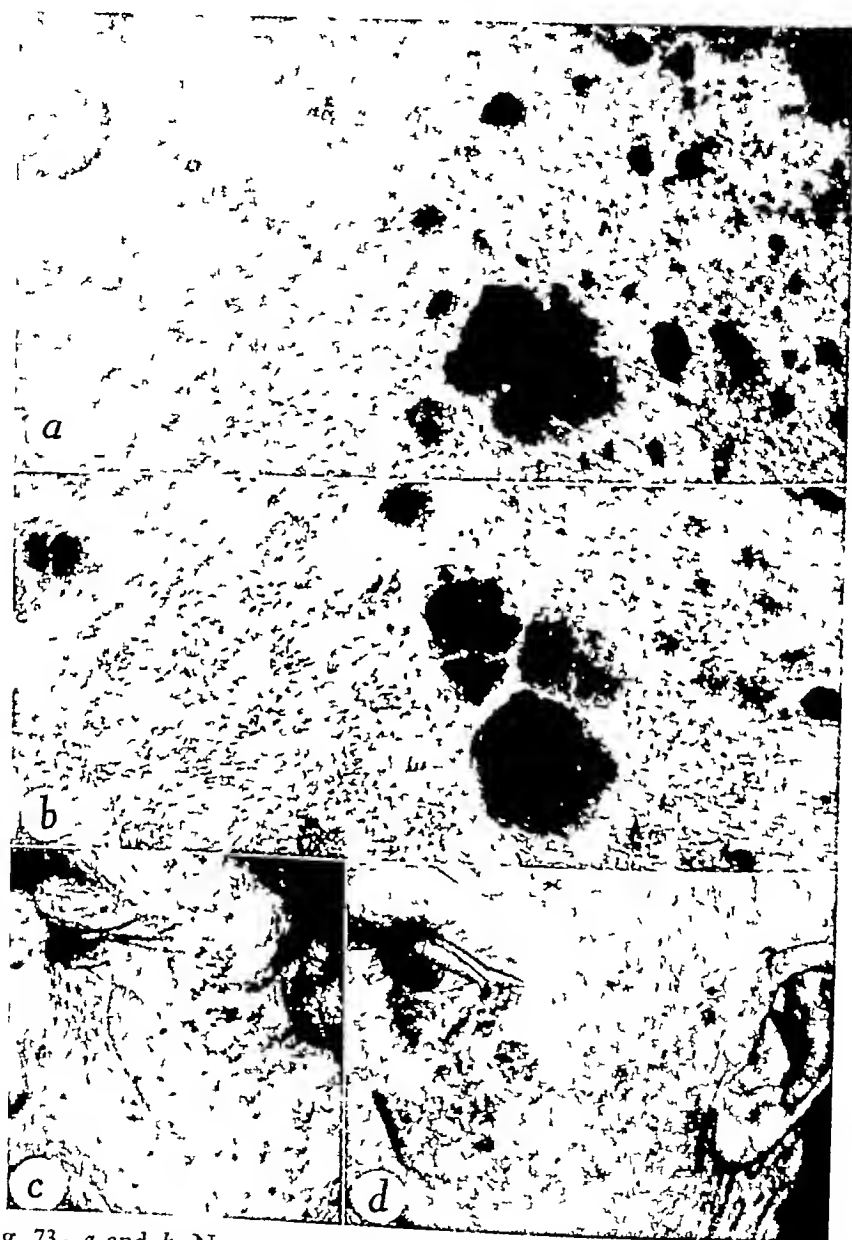


Fig 73—*a* and *b*, Numerous verrucae seniles of the back, varying in size and in degree of pigmentation, some resembling verrucous pigmented nevi. Deeply pigmented lesions simulate melano-epithelioma. *c*, Verruca senilis of the face. Compare with *d*, which depicts keratoma senile and epithelioma arising therefrom.

accompanied by formation of cysts independent of relation to sebaceous glands.

Verruca senilis may be distinguished from verrucous forms of pig-

mented nevi in that the greater part of the lesion of verruca senilis may be removed readily by scrubbing with soap and water. When deeply pigmented or when occurring as solitary black lesions, verrucae seniles also have been confused with melano-epithelioma and blue nevus. Verruca senilis at times may have dry rather than greasy scales and relatively little pigment. This form simulates senile keratosis (Fig 73, *c* and *d*) from which, however, it can be distinguished as a rule by the greater number of lesions and by their larger size, lack of induration or inflammatory reaction and the absence of adherent keratoses. The histopathologic changes are entirely different in the two conditions. Whereas verruca senilis is a benign lesion, senile keratoses are true precancerous lesions. Because of increased formation of melanin pigment, verruca senilis histopathologically has been confused erroneously with pigmented basal cell epithelioma and even with squamous cell epithelioma and melano-epithelioma.

#### MELANO EPITHELIOMA (MELANOCARCINOMA)

Melano-epithelioma usually begins as a solitary, blue black or steel blue, flat or elevated, infiltrated nodule, plaque or tumor, varying from a few millimeters to several centimeters in diameter. Occasionally the color may be a lighter brown, especially when a rapidly growing pigmented nevus undergoes malignant change. Melano-epitheliomas occur on any part of the body but most frequently on the extremities and exposed surfaces. In 30 to 60 per cent of cases melano epitheliomas arise from pigmented nevi. Contrary to what has been stated in the literature, they may arise from both the superficial flat or junction type of nevus and the ordinary hairy mole (Fig 74, *a* and *b*). They arise fairly frequently from lentigines which latter occur especially on the backs of the hands of elderly persons. Lentigo maligna, however which is a deeply pigmented flat macule or slightly raised papule, may remain as such or result in verruca senilis, senile keratosis or melano epithelioma. All types of transitions between lentigines nevi and melano-epithelioma have been described. When melano-epithelioma develops from a pigmented or melanotic spot involving the nail or nail fold it is known as a melanotic whitlow (*paronychia felon*). Fairly frequently melano-epitheliomas develop on the palm or sole some months or years after a puncture wound or other injury. These have been called *implantation melanomas*.

Melano-epitheliomas occur at any age from six months, the average age at onset being fifty years. They are seen more frequently, however among children than other types of epithelioma. The course of melano-epithelioma is varied. There usually is a very rapid increase of size,

the lesion becoming verrucous, fungoid or ulcerative. Fine radiating lines of pigment extending up the lymphatics are indicative of extension. Metastasis may develop early in the disease, frequently skipping adjacent lymph nodes to show involvement of the internal organs. Multiple cutaneous metastatic lesions may be seen and, dependent on the activity of the growth, these metastatic lesions may be pigmented or non-pigmented. Cutaneous metastatic lesions from melanoma of the



Fig 74—*a*, Early melano-epithelioma on the cheek of a boy of ten years arising from a hairy nevus, present since birth, which had been traumatized, subsequent metastasis and death, *b*, melano-epithelioma back of the ear following treatment of a "blood blister" with an electric needle, subsequent metastasis and death (from Ormsby and Montgomery), *c*, typical blue nevus of the hand, *d*, since birth and simulated melano-epithelioma

eye are usually non-pigmented. Melano-epithelioma is characterized histopathologically by the presence of malignant nevus cells.

Not all blue, black or steel blue subcutaneous nodules represent metastatic melano-epithelioma. Such bluish nodules may occur as the result of metastatic carcinoma, sarcoma or lymphoblastoma of various types. Solitary to multiple, firm, bluish nodules either adherent to the skin or lying in subcutaneous tissue and up to 1 cm or more in di-

ameter sometimes result from benign dermatofibroma, including histiocytoma, the color being due to deposits of hemosiderin and to vascularity of the lesion. They may be distinguished by their slow growth and other concomitant findings. A relatively slow growth is also characteristic of dermatofibrosarcoma protuberans, which may appear deep blue as the result of deposits of hemosiderin, and of the early lesions of multiple idiopathic hemorrhagic sarcoma of Kaposi. When one is in doubt, a careful histopathologic examination may be necessary for diagnosis. Distinction of melano-epithelioma from blue nevus, vascular nevi and granuloma pyogenicum is discussed later.

Finally, it may seem absurd to mention large, indolently growing, discrete comedones, or so-called blackheads. Nevertheless, these may attain 0.5 cm. or more in diameter and appear on superficial glance as an indurated, slate black mole. I have had three such lesions referred to me in the past year with an erroneous diagnosis of melano-epithelioma. Careful scrutiny through a hand lens will show the firm, dried-up blackhead within a sebaceous orifice. The blackhead can be picked out with tweezers but is usually resistant to the ordinary method of expression of the smaller comedones.

#### BLUE NEVUS (BLAU NEVUS)

I believe blue nevus to be a relatively common disease as I have encountered more than 100 typical cases. I believe that in the past it has been confused with melano-epithelioma and nevus pigmentosus. Blue nevus is a sharply circumscribed, smooth, round or oval, indurated papule or nodule usually varying from 2 to 15 mm. diameter, occurring most frequently on the face and hands but to be found anywhere on the body. The color varies from dark or mottled blue to blue black, blue gray or even steel blue (Fig. 74, c). There usually is a history of a solitary lesion which either has been present since birth or developed in infancy or early childhood and which has remained as such without increase of size. Such a history is diagnostic. Two or more lesions sometimes occur in the same case. Occasionally, blue nevi develop later in life and, when they are steel blue and have increased in size, they may be indistinguishable clinically from a melano-epithelioma. Wide excision and histopathologic examination then are indicated.

Blue nevus is characterized histopathologically by well-formed, mature dermal dopa positive melanoblasts having long bipolar dendritic processes laden with melanin pigment. Such melanoblasts are found in smaller numbers in so-called Mongolian spot. Mongolian spot is much larger than blue nevus and occurs as an ill-defined, bluish to mulberry colored or blackish plaque, usually in the vicinity of the sacrum

It is present at birth but usually disappears in the third or fourth year of life. Blue nevus is a benign lesion and only exceptionally, following repeated trauma and inflammation, does it undergo malignant change. In such cases it forms a true melanosarcoma rather than a melano-epithelioma.

#### VASCULAR NEVI

Hemangiomas usually develop at birth and are seen in all sizes and shapes from superficial, small spider nevi and port-wine mark nevi, which usually occur on the face, to capillary and cavernous hemangiomas and lymphangiomas. Usually, there is little difficulty in clinical recognition, especially as much of the color can be expressed from the lesion on diascopic pressure with a glass slide. Occasionally, heman-



Fig 75—Granuloma pyogenicum (a, hand, b, ear) resembling melano-epithelioma.

giomas may resemble melano-epithelioma, especially when associated with ulceration and secondary infection (Fig 74, d). Histopathologic studies permit ready differentiation.

**Granuloma Pyogenicum**—This lesion is designated more properly as granuloma telangiectaticum, as histopathologically it may be indistinguishable from an infected hemangioma. Granuloma pyogenicum is confused frequently with melano-epithelioma (Fig 75). Granuloma pyogenicum usually occurs as a single lesion, occasionally as multiple lesions, usually on the extremities and areas exposed to trauma, including the hands, feet and lips. The lesion appears as a pedunculated or sessile tumor a few millimeters to several centimeters in diameter and is blue or blue black. There may be subsequent necrosis and ulceration. The color may be indistinguishable from that of melano-epithe-

lioma The vascular character of the lesions usually suffices for clinical differentiation but histopathologic studies may be necessary at times.

Vascular nevi and also granuloma pyogenicum are essentially benign, rarely undergoing malignant change to hemangio-endothelioma or angiosarcoma.

#### PROGNOSIS AND TREATMENT

The ordinary pigmented nevus is benign and need not be removed except for cosmetic purposes. It is probably good practice, however to remove deeply pigmented nevi, whether flat or elevated, which occur on the sole of the foot or in other regions where they are likely to be subjected to trauma, even though trauma has yet to take place. On the other hand, the occasional nicking of an ordinary hairy pigmented nevus, as in shaving, in my own experience is harmless and does not call for any treatment. If secondary infection supervenes, however then the nevus should be removed as soon as the infection has subsided. If a mole begins to grow rapidly, either with or without increase of pigmentation, and especially if it becomes deep blue even without increase of size, it should be radically removed.

It is common practice, not only among the personnel of beauty shops but also among some physicians, including some dermatologists, to remove pigmented nevi partially by electrolysis and carbon dioxide snow, thus removing most of the pigment and obtaining a scarcely appreciable scar. Nevus cells may remain behind and fibrosis resulting from treatment acts as a source of irritation. I have encountered several cases in which, following incomplete removal of a pigmented nevus by electrolysis or other methods, a melano-epithelioma has developed. Moles should not be treated with roentgen rays or radium, as the nevus cell is not radiosensitive. Dependent on the location and size of the nevus, a simple linear incision following the lines of cleavage of the skin followed by a couple of sutures will usually give an excellent cosmetic result. When pigmented nevi are small they may be removed by adequate diathermy or cautery.

*Verrucae seniles* are benign lesions that are stuck on the skin and, unless they are subjected to repeated trauma malignant changes do not develop in them. They can be removed readily by fulgurating lightly. The resultant scar is almost imperceptible. The epithelial cells in *verruca senilis* are highly differentiated and therefore are resistant to treatment with roentgen rays or radium.

Differences of opinion exist among physicians, including some in various fields, as to whether *melano-epithelioma* should be left disturbed, treated palliatively or radically removed. I believe that lesions described as *melano-epithelioma* that have remained

treatment for many years and have not spread were probably blue nevi that were not recognized as such. Then again, there are borderline cases in which the clinician or the pathologist or both are in doubt regarding the diagnosis of melano-epithelioma. I have encountered several such cases of blue black nevi occurring on the toes in which there has been no recurrence from six to twelve years after a wide excision of the lesion. These could be interpreted as cases of melano-epithelioma that have been cured or, conversely, as cases of melano-epithelioma in which an erroneous histopathologic diagnosis was made. Further histopathologic studies, however, often permit an unequivocal diagnosis of melano-epithelioma to be made. It is in this type of case in which the lesion is observed early that radical excision may be expected to accomplish a cure. Frequently at the time of surgical removal of a melano-epithelioma, even though clinically there is no evidence of lymphatic extension or metastasis, there is already histopathologic evidence of invasion of the lymph and blood vessels by malignant nevus cells. In such cases one can be almost certain either that metastasis has already occurred internally or that cutaneous metastasis may develop far removed from the site of the lesion.

I believe that any pigmented nevus or lentigo (*lentigo maligna*) suspected on clinical grounds of malignant change should be excised radically and widely and the same applies to cases of frank melano-epithelioma before there is evidence of metastasis. Excision may be by the knife, by diathermy or by cautery. In recent series of cases of melano-epithelioma reported separately by Pack and by Cholewick five year survival occurred in from 14 to 20 per cent of the cases respectively. It must be remembered, however, that in cases of melano-epithelioma metastasis and death do not always occur within the first few years. Broders has had one patient who has lived ten years after histologically proved cutaneous metastatic lesions had occurred and fifteen years after operative removal of the primary melano-epithelioma of the eye.

*Blue nevi* should be treated as described for nevus pigmentosus. One should remember that the blue nevus cells are to be found deep in the cutis. When there is evidence of malignant change, wide excision is indicated.

*Vascular nevi*, especially the deeper cavernous types, are more amenable to treatment with roentgen rays and radium than other nevi just described. This also applies to granuloma pyogenicum. Carbon dioxide snow, electrolysis and other measures have been employed in treatment of the port-wine type of nevus. Considerable involution of vascular nevi may result from secondary infection and fairly frequently there is spontaneous involution of the nevi as the child grows older.

Therefore, radical treatment such as excision and grafting can usually be postponed until the child is of an age at which he can co-operate properly or until he has become conscious of the cosmetic defect

### CONCLUSIONS

Careful consideration of clinical and histopathologic findings may be necessary to distinguish different types of nevi from allied conditions and especially from melano epithelioma and hence to arrive at the correct treatment. Blue nevus, which is benign, has been confused frequently with melano-epithelioma. There is danger of malignant change following inadequate removal of benign pigmented nevi. Any nevus that is subject to repeated trauma and irritation or shows increased pigmentation to simulate melano-epithelioma should be radically removed. Hope for cure of melano-epithelioma is dependent on its early recognition and treatment and complete removal before metastasis has occurred.

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# DIABETIC GANGRENE A COMPARISON OF THE PREINSULIN AND INSULIN ERAS

HENRY J LEHNHOFF, JR., EDWARD H RYNEARSON AND  
WILLIAM H BICKEL

BEFORE the discovery of insulin many patients suffering from diabetes died early in the course of the disease Few children survived and a smaller number of patients lived long enough for gangrene to develop These statistics are available in books by such authors as McKittrick and Root,<sup>12</sup> Joslin and his associates<sup>8</sup> and Wilder<sup>23</sup>

This brief report deals with a review of the records of thirty diabetic patients suffering from gangrene of the lower extremities and seen at the Clinic prior to the use of insulin (before 1922) and another group of thirty patients seen in recent years (1937 and 1938) In Table 1, these patients are listed by decades and the increased age at onset of diabetic gangrene of the more recent group is apparent In Table 2,

TABLE 1 —COMPARISON OF PREINSULIN AND INSULIN ERAS AS TO AGE OF ONSET  
OF DIABETIC GANGRENE

Era	Patients by Age of Onset, Years				
	40-49	50-59	60-69	70-79	80-89
Preinsulin	2	16	10	2	0
Insulin	1	8	13	7	1

these patients are classified as to the degree of arteriosclerosis, the extent of the gangrene and the management of these cases It is seen that the patients in the insulin era had lived long enough for more arteriosclerosis to develop and that gangrene had involved more than the toes in a larger number of cases in the insulin era than in the preinsulin era In the preinsulin era five of the patients were sent home without treatment, this does not happen under present-day treatment Of the fourteen patients in the preinsulin era who underwent amputation, six died postoperatively in diabetic coma and one from tetanus Of those who underwent amputation in the years 1937 and 1938, two died of pneumonia, four died of cardiac or renal failure, one died of progressive, massive gangrene and two died of gas gangrene The in-

cidence, prevention and treatment of gas gangrene have been discussed by Macey and one of us (Bickel)<sup>14</sup> The mortality rate in both groups mentioned earlier in this paragraph was high Walters, Meyerding, Judd and Wilder<sup>21</sup> reported a mortality rate of 11 per cent among eighty-six patients who underwent amputation during the years 1922 to 1931, inclusive.

The term "diabetic gangrene" is used inclusively and is understood by all The danger of development of gangrene is the penalty a diabetic patient may pay for living so long Arteriosclerosis is more common among patients suffering from diabetes than among the general population and gangrene too often follows. No one knows why, the hypothesis that the development of diabetic gangrene is related to the fat in the diet has never been proved. Diabetic gangrene occurs no

TABLE 2—DEGREE OF ARTERIOSCLEROSIS AND EXTENT AND MANAGEMENT OF DIABETIC GANGRENE AMONG THIRTY PATIENTS OF THE PREINSULIN ERA AS COMPARED WITH THIRTY PATIENTS OF THE INSULIN ERA

Era	Degree of Arteriosclerosis by Palpation					Extent of Gangrene			Management		
	0	1	2	3	4	Toe	Foot	Leg	Amputation	Medical	Dismissed without Treatment
Preinsulin	8	1	8	13	0	13	15	2	14	11	5
Insulin.	0	3	6	20	1	9	19	2	21	9	0

more frequently among patients on a high fat diet than among those on a high carbohydrate diet (although all diets for patients suffering from diabetes are higher in carbohydrate content in recent years than formerly) Diabetic gangrene practically never occurs except in the lower extremities.

#### PREVENTION OF DIABETIC GANGRENE

The best treatment of diabetic gangrene is prevention and it would be prevented in many instances if the patients would follow the advice given by all specialists on diabetes The following are McKutrick and Root's<sup>12</sup> instructions to patients

**Hygiene of the Foot**—1 Wash feet daily with soap and water thoroughly especially between toes, using pressure rather than rubbing

2 When thoroughly dry rub well with hydrous lanolin as often as necessary to keep skin soft, supple and free from scales and dryness, but not enough to render feet tender. If nails are brittle and div soften by soaking in warm water one-half hour each night and apply lanolin generously under and about nails and bandage loosely. Clean nails with orangewood sticks. Cut the nails only in a good light and after a bath, when the feet are very clean. Cut the nails straight across to avoid injury to the toes. If you go to a chiropodist, tell him you have diabetes.

3 Wear shoes of soft leather which fit and are not tight (neither narrow nor short). Wear new shoes one-half hour only on the first day and increase one hour daily.

4 If the feet become too soft and tender rub once a day with alcohol.

**Treatment of Corns and Callosities**—1 Wear shoes which fit and cause no pressure. The Japanese seldom have gangrene. Beware of nails and torn linings in old shoes and wear new shoes for the first time in the evening. It is wise to have two pairs of shoes which differ slightly from one another and to wear them on successive days.

2 Soak foot in warm, not hot, soapy water. Rub off with gauze or file off dead skin on or about callus or corn. A corn may be painted with the following mixture: Salicylic acid, 1 dram (4 gm), collodion, 1 ounce (30 cc). Repeat for four nights, then, after soaking in warm water, the corn will come off easily. If it does not come off easily without bleeding repeat the treatment for four nights.

3 Do not cut corns or callosities.

4 Wear pad to distribute pressure if necessary. Use felt instead of medicated corn plaster.

5 Prevent calluses under ball of foot.

(a) By exercises such as curling and stretching toes twenty times a day.

(b) By finishing each step on the toes and not on the ball of the foot.

**Circulatory Aids**—1 Exercises. Bend the foot down and up as far as it will go six times. Describe a circle to the left with the foot six times and then to the right. Repeat morning, noon and night.

2 If subject to chilblains wash feet daily in warm water, dry carefully and powder lightly with borated talcum powder. Wear woolen stockings and avoid extremes of temperature.

3 Massage with lanolin.

4 Buerger gravity—hyperemia method for bed patients gives excellent results, as does the violet-ray in indolent sores.

5 Do not wear circular garters.

**Treatment of Abrasions of the Skin**—1 Insignificant injuries in the diabetic may result very seriously. Therefore, proper first-aid treatment is of the utmost importance. Consult your physician.

2 Avoid strong irritating antiseptics, such as sulpho-naphthol and iodine.

3 As soon as possible after injury certain surgeons recommend the application of sterile gauze saturated with medicated alcohol. Keep wet for one hour by pouring on more alcohol. Sterile gauze in sealed packets may be purchased at drug stores. Purchase a tube of boric-acid ointment. Later keep wound covered with boric-acid ointment on sterile gauze. Change daily until healed.

4 Elevate, and as much as possible until recovery, avoid using the foot

5 Consult your doctor for any redness, pain, swelling or other evidence of inflammation

McKittrick and Root<sup>12</sup> also called attention to the use of proper socks, proper shoes and proper arch supports and special shoes

#### TREATMENT OF DIABETIC GANGRENE

In reading representative articles on the subject of amputation<sup>1-7 10 11 13 15-20 22, 24-28</sup> one will see that there are several schools of thought.

There are those who advise immediate and high amputation. These surgeons believe that by so doing they are saving the patient months of time and that the mortality rate is lowest with this operation. There are those who advocate more conservative surgical procedures—amputating one or two toes, for example. Their critics state that too often this simply means one operation after another. (We have seen one patient who had had seven operations on the same leg, each a little higher than the previous one.) Then there are those who advise that unless infection is present no operation should be performed and who state that with time the gangrenous tissue will "drop off" or "slough away" and healing will take place.

In all likelihood, the reader of these articles will reach what is probably a correct impression that there is no rule and that each patient must be judged on his own findings. Certainly a patient who has a small area of gangrene on his toe and whose vessels are easily palpable should *not* have a high amputation, he should have a chance at conservative treatment. Certainly a patient who has a foul smelling infected gangrenous foot and lower leg and none of whose vessels are palpable should *not* be subjected to ridiculous delay. He should have a high amputation. Macey and one of us (Bickel)<sup>14</sup> reviewed the results following amputation of extremities of both diabetic and non-diabetic patients seen at the Mayo Clinic. They called attention to the importance of gas gangrene infection and discussed prophylactic and therapeutic measures to prevent or treat this condition.

Advances in the use of the newer chemotherapeutic agents such as the sulfonamide drugs and penicillin have made the expectant treatment of infected diabetic gangrene much less hazardous than it was previously. Now it is rare to lose a patient who has staphylococcus or streptococcus septicemia, as was likely to happen in earlier days, and immediate high guillotine amputations are not nearly as frequently indicated as they were. If a patient has acute infected gangrene complicated by a cellulitis and lymphangitis, every attempt should be made to bring this process under control before amputation is performed. More rapid healing and a better stump ultimately will be obtained than if amputation were performed while the process was active. The new therapeutic agents, however, have not obviated the dangers from gas gangrene. Many physicians are of the opinion that gas gangrene is less likely to occur when they are used, and that if it does occur it will not be the fulminating type of gas infection which has been encountered so many times in cases of diabetic gangrene. A vigilant watch should be kept for clinical or local signs of gas infection and the treatment of choice should be administered at once. It is in this type of infection that immediate high, open amputation is indicated most frequently.

When time and financial status are not the prime considerations of the patient in whose case infection in a gangrenous extremity is under control, amputation of the affected digits may be tried. Healing is obtained in a sufficient number of cases to make it worth while to try to save the foot. The amputation should always be of the guillotine type or one in which flaps are fashioned and left wide open or approximated by one loose suture. Too often, however, the infection, ulcer or gangrene involves the base of the toes or the sole of the foot in the region of the metatarsal heads and nothing short of amputation of the lower leg is advisable. There are those cases, nevertheless, in which there is infection in the foot with a minimal amount of circulatory obliteration. Such infection will heal with only wide incision and drainage.

In cases of major amputations in which the infection is under control, primary flap amputation below or above the knee without the use of a tourniquet is done. The closure should be loose with interrupted sutures used as sparingly as possible. It is the policy at the Clinic to use a long posterior and a short anterior flap below the knee and a longer anterior than posterior flap above the knee. Rarely is a drain used. Sulfathiazole is sprinkled in the wounds before closure and, in those cases in which infection is feared, a suitable sulfonamide drug is given.

orally after operation. A prophylactic dose of tetanus and gas gangrene antitoxin is always given.

In the matter of conservative treatment, several points bear emphasis. First, heat, but not too much of it, should be applied. These tissues are very susceptible to heat and yet warmth is necessary. Second, antiseptics should be mild. A mixture of equal parts of 50 per cent alcohol and saturated solution of boric acid is satisfactory for wet dressings. Third, exercises of the "Buerger" type are often helpful. Fourth, the "glass boot" has been very disappointing. McKittrick<sup>2</sup> said, "Used under these conditions, we have been unable to satisfy ourselves that pavaex treatment has saved the leg of any of our patients." Fifth, the patient must help decide how long he wishes to try the conservative program. If no infection is present and if his economic circumstances permit, there is no limit to the length of time he can wait—and often he will be repaid. Finally, many of these patients are elderly and many are greatly dehydrated and are suffering from diabetic acidosis. Take time, if you can, to restore such a man's condition.

#### CONCLUSIONS

1 Insulin has enabled diabetic patients to live longer than before its introduction and an increased incidence of arteriosclerosis and gangrene is to be expected.

2 With modern treatment diabetic coma should not develop following any operation, coma was the chief cause of death during the pre-insulin era.

3 The occurrence of gas gangrene is a dangerous postoperative complication.

4 The prevention of gangrene is more important than its treatment.

5 Every patient who has diabetic gangrene must have an individual appraisal before one decides as to treatment, there are no "rules."

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# HYPERINSULINISM THE USE AND MISUSE OF THE TERM

MELVIN T GORSUCH AND EDWARD H RYNearson

HYPERINSULINISM was first described by Seale Harris<sup>1</sup> in 1924. Since then the literature has contained many references to this condition. We are attempting in this brief discussion, first, to define hyperinsulinism, and second, to distinguish this condition from the broad field of spontaneous hypoglycemia.

The term "hyperinsulinism" should be restricted to the condition produced by an excessive amount of insulin. Induced hyperinsulinism needs no elaboration, it is the typical insulin reaction, familiar to all physicians interested in the treatment of diabetes. Spontaneous or true hyperinsulinism is a very rare syndrome. We feel that this term should be used only in those cases in which an adenoma or carcinoma originating in the cells of the islands of Langerhans is found at operation or at necropsy. In all other cases in which hypoglycemia is present, the condition should be diagnosed as "spontaneous hypoglycemia" rather than as "hyperinsulinism."

Hypoglycemia may occur in association with certain deficiencies of the pituitary body, the thyroid gland or of the suprarenal glands, with destruction of the liver, and with functional or organic disturbances of the nervous system. A review of the medical literature discloses a large number of cases of nervous or functional hypoglycemia. Usually the patient is emotionally unstable, and one is impressed by the nervous anxiety and tension state depicted. In a significant number of cases, hyperirritability of the autonomic nervous system with features of vagus nerve predominance is suggested. We are unwilling to accept the suggestion that these are representative instances of an excessive production of endogenous insulin. Keating and Wilder<sup>2</sup> have stated that in this group of cases there may be an abnormal depression of the concentration of blood sugar owing to stimulation of nerves or the liver or, an exaggeration of ordinary physiologic fluctuations in the concentration of the blood sugar owing to tension or anxiety, or, that an abnormal sensitivity of the individual to physiologic excursions of the concentration of blood sugar may be responsible.

Although in a review of the literature we found such terms as "diabetes insulinitis," chronic hypoglycemia, and "functional hyperinsulinism," we believe that the terms hyperinsulinism and spontaneous hypoglycemia are sufficiently descriptive.



The accompanying tabulation shows the etiologic factors in eighty-five cases that were observed at the Clinic in a period of three years, that is from January 1, 1940 to December 31, 1942. In the twenty-one cases in which hyperinsulinism was due to administration of excessive

ETIOLOGIC CLASSIFICATION OF EIGHTY-FIVE CASES OF HYPERINSULINISM AND  
SPONTANEOUS HYPOGLYCEMIA

<i>Hyperinsulinism</i>	Cases
Administration of excessive amounts of insulin	21
Tumor of the islands of Langerhans	10
<i>Spontaneous hypoglycemia</i>	
Nervous or functional	41
Hepatic origin (not proved)	2
Simmonds' cachexia	1
Addison's disease	1
Cerebral degeneration	1
Pernicious anemia (exploratory operation disclosed no abnormality)	1
Indeterminate (exploratory operation disclosed no abnormality)	4
Indeterminate (no exploratory operation)	3
Total	<hr/> 85

amounts of insulin, the patients were referred to the Clinic because the hyperinsulinism was a major problem in the control of diabetes. This group does not include any case in which the patient had an occasional reaction to insulin. The symptoms and diagnosis of hyperinsulinism that is due to the administration of excessive amounts of insulin are too well known to warrant further consideration.

Tumors of the islands of Langerhans were found in ten cases. This is by far the most interesting group and is quite distinct from the fifty-four cases in which the patients were suffering from spontaneous hypoglycemia. A few patients in the latter group were found to have hypoglycemia as part of, or in association with, other diseases. In seven cases the cause of the hypoglycemia is listed as indeterminate. In forty-one cases, a diagnosis of nervous or functional hypoglycemia was made.

As an illustration of the history and findings in the cases in which a tumor of the islands of Langerhans was found, the following case is reported.

CASE I—A female secretary, aged thirty-two years, was admitted to St. Mary's Hospital on October 19, 1942. The patient had been in excellent health until two years prior to this admission, when she first had noted an increasing number of errors in her stenographic work. She had discovered that eating frequently reduced these errors and would relieve her other symptoms of impaired concentration, mental confusion and sensations of unreality. Three months after the onset of this illness she had her first episode of unconsciousness. While she had

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been Christmas shopping she had noted weakness, dizziness and recurrent episodes of disorientation, followed by unconsciousness. She had remained comatose for six hours, recovery had been spontaneous. Because her family had been unable to awaken her in the morning two days later, the patient had been admitted to a hospital. She had remained comatose until 4 P.M. of the following day at which time the intravenous administration of dextrose had produced immediate recovery. A diagnosis of hypoglycemia of indeterminate origin had been made. The value for the fasting blood sugar had been found to be 95 mg. per 100 cc. immediately before a glucose tolerance test had been performed. The values for the blood sugar had been found to be 195 mg., 333 mg., 174 mg. and 160 mg., respectively, one, two, three and four hours after the oral administration of 100 gm. dextrose. During the next three months, the values for the blood sugar had ranged from 45 to 75 mg. per 100 cc.

Various types of treatment had been tried, including a high fat diet, a high protein diet, a high carbohydrate diet, injections of solution of posterior pituitary and subcutaneous injections of 1 cc. of epinephrine in oil twice daily. In addition to her meals and intermediate feedings the patient had drunk the juice of three dozen oranges at intervals during each twenty four hours. On such a regimen she had gained 45 pounds (20.4 kg.) but she had continued to have the following symptoms: diplopia, paresthesias of the face and extremities, difficulty in awakening, extreme exhaustion in the early morning hours, and impaired concentration.

When the patient was admitted to St. Mary's Hospital, the results of physical examination were essentially negative, except for the presence of obesity. After the administration of a glass of orange juice at 5 A.M., a fasting test for hypoglycemia was begun. The values for the blood sugar at 8 and 11 A.M., and at 2 P.M. were 54, 34 and 25 mg. per 100 cc. respectively. Mental confusion was noted at 11 A.M., and at 12:30 P.M., the patient was unresponsive. At 1 P.M. the patient was having severe generalized convulsions. Intravenous administration of 2.5 g. of dextrose was followed by complete relief of the hypoglycemic symptoms.

On October 27, 1942, an adenocarcinoma, grade 1, of the islets of Langerhans, which measured 1.5 by 1 by 1 cm., was removed. Convalescence was complicated by pulmonary congestion and the development of a pancreatic fistula. The patient was dismissed on the nineteenth day after operation. She has written letters stating that she has not experienced any recurrence of her hypoglycemic symptoms and is feeling entirely well.

There are several points in this history which are worthy of emphasis. The patient, who formerly had been very stable, became unstable. The patient's symptoms were present when feedings were delayed or when she exercised, as in shopping, and all of the symptoms were promptly relieved by the ingestion of food or by the administration of dextrose. Complete recovery followed the successful surgical removal of the insulin producing tumor.

In the following case the symptoms were similar to those in Case 1 but operation did not disclose any abnormality.

CASE 11.—A white man, aged thirty-eight years, registered at the Clinic on May 5, 1942. For ten years he had experienced episodes of mild indigestion

Except for these attacks he had enjoyed good health until a year and a half before he came to the Clinic. He then had begun to have attacks characterized by weakness, giddiness, perspiration, blurred vision, and amnesia. On two occasions he had lost consciousness. Six months before he came to the Clinic, his wife had been unable to awaken him at 11 A.M., which was his usual time for arising while working on the night shift. His wife said that on this occasion he had been "groggy," pale, and only slightly responsive. There had been fixation of gaze and grunting respirations, and his body had been moist with perspiration. From this semistuporous state he had sunk into a deep slumber from which he could not be awakened until 4 P.M. After this attack he had had weekly attacks which had been less severe than the previous attack and had not been associated with loss of consciousness. During these episodes his wife had noted that the patient was confused, belligerent, and walked with a staggering gait. Talking in a loud voice and automatic behavior also had been observed. The majority of these episodes had occurred during the early morning hours if his breakfast had been delayed or omitted. He had been advised to eat more carbohydrate at the time of his regular meals, but had not partaken of any intermediate feedings. During one episode, dextrose was given intravenously to restore consciousness.

The patient was transferred to St. Mary's Hospital for special metabolic studies. The value for the fasting blood sugar, which was determined just before an Exton-Rose glucose tolerance test was started, was 49 mg per 100 cc. The glucose tolerance disclosed the following values for the blood sugar: 69 mg per 100 cc at the end of half an hour and 81 mg per 100 cc at the end of one hour. After the patient had fasted for twenty-four hours the value for the blood sugar was 45 mg per 100 cc and the usual symptoms of hypoglycemia were present.

An exploratory operation was performed but careful inspection and palpation of the pancreas failed to reveal any abnormality. Microscopic examination of two small sections of the pancreas disclosed only normal pancreatic tissue. A dietary regimen, which included feedings between meals, was prescribed. The patient was permitted to return to his home but was requested to return to the Clinic in four months.

When he returned to the Clinic, he stated that he had had no symptoms during this interval. When the patient returned to the Clinic, the value for the blood sugar was 88 mg per 100 cc.

In Case II, the hypoglycemic symptoms were sufficiently severe to warrant surgical exploration. The fact that frequent feedings completely relieved the symptoms raises the question as to whether medical treatment could not have been prescribed without the operation. This would have been unwise since all tumors of the island cells must be regarded as either malignant or "pre-malignant." There is, as yet, no method of determining the presence or absence of a tumor except by operation.

In the following case of nervous or functional hypoglycemia, the history and findings are in marked contrast with those in the two previous cases.

CASE III—A housewife aged sixty-one years, had had recurring attacks of impaired concentration, headache, dimness of vision, irritability, tremors of the hands, generalized weakness, and perspiration since childhood. These attacks usually had occurred at 10 A.M. and 3 P.M. No hypoglycemic symptoms had been experienced as a result of a night's fast. Food, and particularly coffee, had produced instantaneous relief from these symptoms. The patient always had been obese. One year before she came to the Clinic she had experienced hypoglycemic symptoms during the performance of a glucose tolerance test, and since then she had felt justified in eating with more abandon. Obesity was her chief concern.

The general symptoms gave further evidence of instability of the autonomic nervous system. Food idiosyncrasies were prominent and the partaking of certain foods invariably had been accompanied by eczema and urticaria. She had had relatively infrequent and irregularly recurring attacks of diarrhea which had been associated with dull aching in the cecal and sigmoid regions of the abdomen. A feeling of abdominal tension and "bloating" after meals had been a constant symptom. She had been extremely sensitive to cold. Cardiac irregularity had been a subjective sensation; this disturbance had been relieved by food.

An electrocardiogram revealed sinus bradycardia, a cardiac rate of 54, and occasional premature auricular contractions. Vagal release was effected by the administration of atropine. Immediately before the oral administration of 90 gm. of dextrose for an ordinary glucose tolerance test, the value for the fasting blood sugar was found to be 100 mg per 100 cc. The glucose tolerance test revealed the following values for the blood sugar: 188 mg per 100 cc. at the end of half an hour, 154 mg per 100 cc. at the end of two hours, 170 mg per 100 cc. at the end of two and a half hours, 93 mg per 100 cc. at the end of three hours, 72 mg per 100 cc. at the end of four hours and 89 mg per 100 cc. at the end of six hours. At the end of four hours, the patient had mild hypoglycemic symptoms, including cold perspiration and slight mental confusion. A fasting test for hypoglycemia was continued for thirty-two hours. At the end of this period, the value for the blood sugar was 111 mg per 100 cc. The patient did not have any symptoms of hypoglycemia during this period.

The patient returned to the Clinic after an absence of five months. During this interval the patient had been eating six times a day and the diet had furnished a total of 1100 calories daily. This dietetic regimen had afforded complete relief from hypoglycemic symptoms and had produced a noticeable reduction in weight.

The interesting points in this case are the number of associated functional symptoms, some of which had been present since childhood, the "indefinite" history as contrasted with the clear-cut history of true hyperinsulinism, the absence of severe hypoglycemia at any time, the normal concentration of blood sugar and absence of symptoms, after a prolonged fast.

This patient and the other forty patients who had nervous or functional hypoglycemia did not require an operation. Many of them more in need of a frank discussion and discipline. Thirteen of the one patients had an associated neurosis, anxiety state of hypox

asis and three patients had an associated epilepsy. Very few of the patients in this entire group had stable personalities. Most of their symptoms were more related to the sympathetic nervous system than to the concentration of the blood sugar. In only twenty-four cases was mention made of the restorative effect of dextrose, in seventeen cases, improvement was inconstant and questionable, in six cases, relief was definite, and in one case, the dextrose had no effect. Twenty-nine patients had experienced no difficulty at night. None except those with epilepsy had had convulsive seizures.

Probably the most important test in distinguishing severe hypoglycemia from the functional or nervous type is the prolonged fast. Very few patients with hyperinsulinism can fast very long, particularly if exercise is employed. Patients with severe hyperinsulinism cannot fast for longer than two or three hours. This test has proved of more value than has the glucose tolerance test. Very often, the sugar tolerance curve is typical of diabetes, rather than "flat," in cases of proved hyperinsulinism. Portis and Zitman<sup>3</sup> found "flat" curves in neuropsychiatric cases.

Finally, it should be stated that in these forty-one cases of functional or nervous hypoglycemia hyperinsulinism was diagnosed or suspected. This does not include the many strictly nervous patients who, as part of their nervousness, frequently ate food or candy or drank carbonated beverages.

#### SUMMARY AND CONCLUSIONS

Hypoglycemia can be related to many functional or pathologic disturbances. The term "hyperinsulinism" should be used only in cases in which the symptoms are caused by an excessive amount of insulin, either exogenous or endogenous. The term "hyperinsulinism" should not be abused by applying it to hypoglycemia that may be due to any one of many causes. True hyperinsulinism resulting from a tumor of the islands of Langerhans is very rare, the spontaneous hypoglycemia of the nervous individual is much more common.

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## EXPERIENCE IN THE CARE OF ASTHMATIC PATIENTS UNDERGOING OPERATION BASED ON 142 CASES

LOUIS E. PRICKMAN AND PHILIP D. GELBACH

SURGICAL procedures on patients who have, or who have had asthma, must be approached with caution and only after precautions have been taken. The person who has asthma usually coughs a great deal, is unable because of dyspnea to lie flat in bed and is not in suitable condition for surgical procedures until the cough and asthma can be brought under control. Moreover many asthmatic patients have varying amounts of chronic bronchitis which may be a forerunner of pulmonary complications under conditions of anesthesia and operation. An exception to these general statements should be indicated at the outset, namely that asthmatic patients tolerate operations on the nose and sinuses with comparative ease and safety. Coughing and orthopnea need not interfere seriously with convalescence after such operations and then too they are usually carried out with the patient under local anesthesia.

Coughing is an intimate part of the asthma syndrome. Coughing in asthma is a protective procedure designed either to remove an accumulation of excessive bronchial secretion, or to protect the patient from inhaling noxious substances, such as excessively cold or hot air, fumes, smoke, house dust, irritating inhalants like powder, dusts of feathers, danders, and countless other similar substances. When such substances are inhaled, coughing begins and is followed by bronchial secretion and bronchospasm or edema by means of which nature hopes to forestall inhalation and absorption of the noxious material.

In asthmatic bronchitis bronchial secretions protect the surface of irritated bronchi, but they usually are present in excessive amounts especially in the morning. Under normal conditions bronchial secretions are not permitted to accumulate but are removed by action of cilia. In asthmatic bronchitis, cilia are ineffectual in removing accumulations of thick tenacious bronchial secretions and hard coughing is necessary to remove such material. Secretions allowed to accumulate and stagnate in bronchi may be forerunners of such complications as acute bronchitis, localized pneumonitis, bronchostenosis and pneumonia.

Important and necessary as coughing is under the circumstances just mentioned it is likewise hazardous under conditions of operation. Convalescence after operations. When bronchial secretions are in excess after operations, it is necessary to move the pa-

from one side to the other and encourage coughing in order to raise the secretions. This protective coughing, however, is hazardous to suture lines, causes great pain and discomfort to the patient, and may result in loss of the benefit of an otherwise satisfactory surgical procedure. Just as the coughing of the asthmatic patient occasionally may precipitate the formation of inguinal and femoral hernias by sudden increases in the intra-abdominal pressure, the same coughing after operation interferes with strong surgical repair of hernial, or other incisions in the abdominal wall.

Experience shows that there are correct and incorrect ways of attempting to control the cough associated with asthma. It is incorrect and dangerous to resort to morphine, or codeine and related products which suppress coughing by depressing the respiratory center. By so doing, secretions are allowed to accumulate and stagnate in the bronchi and various pulmonary complications may result. As has been stated, coughing is a protective mechanism in asthma, even though coughing usually makes any attack of asthma more severe. The proper way to control cough in asthma, and thereby make operations on asthmatic patients comparatively safe, is to remove the cause of the coughing and not try to suppress the cough itself. This is an important principle, and is the secret to successful operations on asthmatic patients. Unfortunately, to remove the cause of coughing and asthma is easier said than done, but certain procedures and principles if understood and carefully followed will permit control of coughing and asthma of many patients. The most important of these principles and procedures will now be considered.

For simplicity, the causes of asthma will be discussed briefly under the two main headings of allergic asthma and infectious asthma or asthmatic bronchitis. A given case of asthma may be caused by both allergic and infectious factors. Neurogenic causes of asthma, always important in evaluating any case of asthma, need not be considered herein except to state that if present, nervous factors should be sought and removed or controlled, if at all possible.

### ALLERGIC ASTHMA

The patient who has allergic asthma (extrinsic) must have both a careful general examination and allergic survey before an operation. The latter is necessary because the first principle in the successful treatment of the allergic patient is to ascertain and then remove from his environment every substance (inhalants, ingesta, drugs, and so on) to which the patient is sensitive. Removal of these substances

is comparatively easy in most hospitals, where dusts are not present in quantity. A reasonably dust-free room is accomplished by removing rugs, dusty draperies and cushions, by covering pillows and mattress with dust-proof coverings and by restricting dusting powder and other cosmetics to those best tolerated by the patient.

If the patient has asthma as a complication of hay fever (pollinosis) and has to be operated on during the hay fever season, it is necessary that he be placed in a pollen-free room in the hospital for both pre-operative and postoperative care. A number of efficient pollen filters have been manufactured, any one of which can be placed in the patient's window in the hospital and the air filtered if the room is not otherwise air conditioned. After the patient has spent a few days in such a room all traces of asthma disappear if pollen is its sole cause. Obviously the patient must be returned to a pollen-free room after the operation, to remain during his convalescence.

Most hospital rooms are ideal environment for patients who have other types of extrinsic asthma too. They are protected from danders, house dust, feathers and cosmetic irritants if the proper precautions are taken and usually after a few days' hospitalization, coughing, orthopnea and asthma are no longer hazards to operation.

Patients having asthma usually are oppressed by high humidity and by sudden changes of temperature. Air-conditioned rooms are not always comfortable for them. A room with a comfortable and constant temperature free from draft is desirable. A fan is generally undesirable but if conditions demand its use it is best placed under the patient's bed and not run at a high speed.

The diet of these patients should be planned with several principles in mind, only two of which will be emphasized. First, it is obvious that any food to which the patient is known to be sensitive or to which he is suspected of being sensitive should not appear in his diet. Second, because the asthmatic patient's breathing is further handicapped by large meals or by foods which cause him to feel distended, the pre-operative and postoperative diet should be bland and the quantity of food at the evening meal particularly should be "light."

While we are considering the matter of food and drink it seems important to emphasize that all patients should be questioned carefully about idiosyncrasies to various drugs such as acetylsalicylic acid (aspirin), morphine and barbiturates. If such idiosyncrasies do exist, all charts and records should be marked plainly so that physicians and the nursing staff may be cautioned against the administration of such drugs.



## ASTHMATIC BRONCHITIS

The second and larger group of cases of asthma are those in which infection (asthmatic bronchitis, or infectious asthma) is the causative factor. In some cases of allergic asthma bronchitis is associated, or is secondary. In asthmatic bronchitis and in bronchitis complicating allergic asthma, the bronchial membranes present varying degrees of inflammation, edema, erythema, secretion of mucus and narrowing of the lumen. Coughing, expectoration, wheezing, and orthopnea in varying degrees result from those pathologic changes. In order to control these symptoms which forbid most operations except at unjustified risk, it is necessary to allow and to aid the underlying bronchitis to subside before proceeding with anesthesia and operation. Many lives have been and can be prolonged and surgical morbidity and mortality kept low by refusing to sanction surgical operation, or by postponing operation in cases of asthmatic bronchitis until the patients can be properly prepared.

In order to promote healing of inflammation in the bronchi as seen in asthmatic bronchitis, rest is needed. The longer the bronchitis has existed, the longer the rest that will be required to allow the inflammation to subside. Just as in pulmonary tuberculosis, rest in bed is the quickest way to get results, although most patients are reluctant or unable to consider such a drastic change in their way of living. By complete rest in bed, however, cough is brought most quickly under control. Coughing irritates bronchi which are inflamed and interferes with healing just as constant irritation of an ulcer or of a wound interferes with healing. Coughing and dyspnea can be minimized by avoiding exertion, coryza, hard laughing, sudden changes of temperature, dust, smoke, and other respiratory irritants. Proper humidity in the home and especially the sleeping room during the winter months is important. The sleeping room should be warm and comfortable and preferably ventilated from an adjoining room. Useful medication includes expectorants, particularly the iodides, and the unstinted use of epinephrine, ephedrine, neosynephrine or propadrine hydrochloride for early symptomatic relief of asthma before hard coughing and a severe paroxysm of asthma result.

The patient who has asthmatic bronchitis presents a most difficult problem from the standpoint of preparation for operation and of assuring a smooth postoperative convalescence. Most careful general examination is important. The role of nasal and sinus infections must be investigated and if, for instance, the sinuses are found to be infected, adequate drainage should be established and the reaction from this operation allowed to subside before the general surgical problem is attacked.

## OPERATIVE CARE OF ASTHMATIC PATIENTS

Roentgen examinations of the thorax and examinations of the sputum are always necessary. The degree of emphysema present is highly significant, as much emphysema contraindicates many surgical procedures.

The preparation for operation in cases of asthmatic bronchitis requires time and patience and cannot be hurried. Frequently it is necessary to wait for a more favorable warm season. When older patients have asthma, bronchitis is usually the underlying cause, and a combination of increased age and accompanying bronchitis increases the surgical risk. Observation in the hospital of patients who have asthmatic bronchitis is frequently desirable in order better to evaluate the degree of bronchitis and the patient's response to treatment before the final decision for or against operation is made. If the cough subsides and is no longer a problem, if the patient can lie comfortably flat in bed all night, and if there has not been a recent acute respiratory infection, necessary surgical procedures may be considered.

### TREATMENT AFTER OPERATION

When pulmonary complications develop postoperatively, they should be recognized and treated early. Inhalation (mask or tent) of oxygen or helium and oxygen, hourly brief inhalations of carbon dioxide to promote full inflation of the lung and to combat atelectasis, and the moving of the patient from one side to the other every two hours are important precautions to take. Frequent subcutaneous use of epinephrine in quantities of 6 minims, supplemented by aminophylline, in doses of  $3\frac{3}{4}$  to  $7\frac{1}{2}$  grains (0.25 to 0.5 gm.) given intravenously or by rectum will usually control asthma. Iodides may be administered by rectum until the patient is eating, and they then may be given orally for their expectorant effect. In an occasional instance bronchoscopy may be indicated for postoperative atelectasis when other measures fail. Chemotherapy is of proved value in pulmonary infections, and in some instances should be given a few days before operation and when necessary can be given after operation.

The following brief case reports exemplify the value of sulfonamide therapy in reducing morbidity of postoperative pulmonary complications of patients who have asthma. In the first case cough and fever (to  $102^{\circ}\text{F}$ ) developed on the eighth postoperative day and the patient exhibited clinical and roentgenologic findings of pneumonia of the right upper lobe. Bacteriologic examination of the sputum revealed positive Neufeld reaction (Group B pneumococcus). Sulfathiazole therapy was instituted at once and continued for six days. On the eleventh postoperative day temperature was normal and it remained so. Convalescence was otherwise uneventful. In the second case fever

(to 101.4° F) and a productive cough developed on the second postoperative day. The patient's thorax was full of moist rales, but there were no definite areas of consolidation. Administration of sulfathiazole was begun and continued through the sixth postoperative day at which time the symptoms and signs had completely disappeared.

In a third case pneumonia of the left lower lobe developed on the fourth postoperative day. Administration of sulfathiazole was started at once and continued through the ninth postoperative day. The patient was subjectively improved and his temperature was normal on the seventh postoperative day. His recovery was otherwise uneventful. In a fourth case massive atelectasis of the left lung with fever (to 103.6° F) developed on the third day after operation. Bronchoscopy was done and the patient was somewhat improved the following day. Sulfathiazole therapy was started on the fifth postoperative day because of continued fever and the clinical signs of a residual inflammation of the left lung. Chemotherapy was continued through the ninth day after operation. The patient's temperature was normal on the eighth postoperative day and his recovery was satisfactory.

#### INCIDENCE OF POSTOPERATIVE COMPLICATIONS IN THIS AND PREVIOUS SERIES

In a previous study of the surgical risk of asthma, Gaarde, one of us (LEP) and Raszkowski showed that the most common postoperative pulmonary complications in their series include pneumonia (5 per cent), severe asthma (5 per cent), bronchitis (2 per cent), atelectasis (1 per cent) and pulmonary infarction (less than 1 per cent). The records of consecutive patients who had or had had asthma and were subjected to major surgical procedures at the Clinic from July, 1934, to September, 1940, comprised their series. We have reviewed our experience with a series of 142 consecutive cases of asthma in which major surgical procedures were performed at the Clinic between September, 1940, and July, 1943, to study further the incidence of postoperative pulmonary complications and the mortality risk in this group of patients. Because, at the time of operation in our group of cases the treatment of pulmonary infections with sulfonamide compounds was almost routine, we were interested particularly in determining what effect treatment with these drugs would have on the incidence of postoperative pulmonary complications. So many additional factors were involved, however, that no conclusions relative to sulfonamide therapy alone may be drawn safely. There can be no question, however, that in handling postoperative pneumonia and bronchitis chemotherapy is most valuable tool.

# OPERATIVE CARE OF ASTHMATIC PATIENTS

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In this study of 142 cases as in the previous study mentioned, severe bronchial asthma was included as a postoperative pulmonary complication. A number of patients had mild or moderate asthma during the

## POSTOPERATIVE PULMONARY COMPLICATIONS IN 142 CASES OF ASTHMA

Site of Operation or Condition Present	Cases	Postoperative Pulmonary Complications					Death
		Pneumonia	Atelectasis	Severe Asthma	Bronchitis	Total	
Upper part of abdomen	24	2	2			6	
Gallbladder	18	2	2		2	4	1
Stomach and duodenum	30			1		2	
Lower part of abdomen	15		1		1	3	
Pelvis	5		1		2	1	
Hernia (inguinal)	3					1	
Colon						1	
Appendix						1	
Sites other than abdomen	12					1	
Breast	18		1			1	
Thyroid	1					1	
Prostate	5			1		2	
Central nervous system	4					1	
Kidney	1					1	
Amputation through mid thigh	6					1	
Miscellaneous conditions	142	6	4	6	22	38	13
Total							
Per cent of total		4	3	4	15	26	9

Miscellaneous conditions consisted of one case each of excision of multiple lipomas, excision of melanoma of foot and skin graft, amputation of penis and radical dissection of penis, radical block dissection of left side of neck for epithelioma of the lip, excision of wart, and removal of large brachial cyst.

postoperative period, but it was no worse than that which they had had in the preoperative period. We did not feel therefore, that their asthma constituted a postoperative pulmonary complication.

Of the 142 patients in this study, 102 (72 per cent) were classified as having asthmatic bronchitis, thirty-two (23 per cent) as having allergic asthma, and eight (5 per cent) as having mixed asthma (allergic asthma complicated by bronchitis). In twenty-two (15 per cent) of the 142 cases some form of pulmonary complication (including severe asthma) developed after operation as is shown in the accompanying table. There were six cases of postoperative pneumonia, six of atelectasis, six of bronchitis and four of severe asthma. Of the twenty-two cases of postoperative pulmonary complications, the preoperative diagnosis in fifteen (68 per cent) was asthmatic bronchitis, in four (18 per cent) allergic asthma, and in three (14 per cent) combined or mixed type of asthma. In all six cases in which pneumonia developed the preoperative diagnosis was asthmatic bronchitis. Atelectasis occurred in four cases of asthmatic bronchitis, in one case of allergic asthma and in one of mixed type of asthma. Of the six cases in which bronchitis developed postoperatively, the incidence of types of asthma was the same as that in the cases in which atelectasis developed. Severe asthma occurred postoperatively in two cases of allergic asthma, in one case of asthmatic bronchitis, and in one of a mixed type of asthma.

Certain types of surgical procedures are more hazardous to the asthmatic patient than others. It has been estimated that pulmonary complications occur twice as frequently in operations on the upper part of the abdomen as in operations on the lower part of the abdomen because splinting of the diaphragm and lower muscles of the thorax materially reduces the vital capacity and interferes with aeration of the adjacent lung and with bronchial drainage. Gaarde, one of us (L. E. P.) and Raszkowski have shown that the incidence of pulmonary complications after operations on the upper part of the abdomen was 24.5 per cent or three times higher than after operations on the lower part of the abdomen (7 per cent). In our study pulmonary complications developed in 24 per cent of the cases of asthma in which upper abdominal operations were performed and in 13 per cent of the cases in which operations were on the lower part of the abdomen. In asthma, therefore, operations on the biliary tract and stomach must be exceptionally well considered from all standpoints.

#### MORTALITY RATE IN OUR SERIES

In the entire group of 142 cases in which the diagnosis of asthma had been made previous to operation, two deaths occurred, a mortality of 1.4 per cent.

CASE I—The patient, a farmer aged fifty-one years, had come to the Clinic two times previous to his last registration because of left renal lithiasis. On these admissions because of persistent asthmatic bronchitis complicated by emphysema conservative treatment of the renal lithiasis was considered the procedure of choice in preference to the risk of operation. On his third admission the patient stated that he had had so many attacks of chills, fever and renal colic that he wished to assume the high risk of operation which was recognized by all. He was hospitalized for a period of preoperative treatment for asthma. During this time bronchoscopy which gave negative results was done because the history and findings relative to the air passages suggested the possibility of a bronchostenotic lesion. It was impossible completely to control his asthma and cough before operation, but when he was in as good condition as possible left nephrectomy was done under spinal anesthesia.

On the sixth postoperative day clinical signs suggesting early pneumonia of the left lower lobe developed. Sulfonamide therapy had to be discontinued on the eighth postoperative day because of marked reduction of urinary output. Determination of the urea in the blood revealed 152 mg per 100 cc. at this time. In spite of all supportive measures death occurred on the eighth postoperative day.

Necropsy findings revealed moderate emphysema of the lungs and the bronchi and their branches were filled with mucous plugs. There was no evidence of definite pneumonia. It seems reasonable to suspect that renal insufficiency was a large factor in the death of this patient.

CASE II—The patient was a man, aged thirty-nine years, who had had hay fever and asthma for twenty years. His most severe asthma occurred during the hay fever season (ragweed) but he had mild perennial asthma presumably on the basis of asthmatic bronchitis. Routine roentgenograms of the thorax revealed a shadow of increased density behind the heart on the left, which on further study was diagnosed as intramural leiomyoma of the lower end of the esophagus. Exploration was advised and he was admitted to the hospital for a few days preoperative preparation which included doses of iodides and 60 grains (4 gm.) of sulfadiazine on the day before operation.

Transpleural resection of the lower 7 inches (17.8 cm.) of the esophagus and cardiac end of the stomach and transposition of the stomach into the thoracic cavity with anastomosis of the lower end of the esophagus into the anterior wall of the stomach was done under nitrous oxide oxygen carbon dioxide ether and cyclopropane anesthesia. A leiomyoma of the lower part of the esophagus and gastric cardia was found at operation. The patient's condition was good on the first postoperative day but on the second day he became comatose and could not be aroused. He had no definite asthma, but in spite of all supportive efforts his temperature gradually rose and he died on the third postoperative day.

Postmortem examination revealed left hemorrhagic hydrothorax (250 cc) and moderate atelectasis of all lobes of the lungs. There was a hemorrhagic exudate in most of the bronchi, and the left lower lobe bronchus was occluded by a heavy exudate containing many polymorphonuclear leukocytes.

Case II certainly must be classified as a postoperative pulmonary death, but it is reasonable to assume that the nature of the surgical procedure contributed to the collapse of the lungs found at necropsy.

The types of anesthetic agents used in this series varied considerably. In asthmatic bronchitis ether anesthesia was avoided whenever feasible, in favor of spinal or intravenous anesthesia. However, when ether anesthesia would seem definitely to shorten and simplify the operative procedure, it should be considered rather than another type of anesthesia which would not give the optimum of operative facilities. In this study fifty-eight patients who had asthma were given ether anesthesia in conjunction with other anesthetic agents. Pulmonary complications developed after operation in ten (17 per cent) of these cases.

#### SUMMARY

The preoperative and postoperative care of patients who have or who have had asthma and require surgical procedure, has been reviewed. With adequate preoperative and postoperative precautions the risk of operation is not great, inasmuch as 85 per cent of our patients underwent major surgical procedures without significant pulmonary complications, and 98.7 per cent survived the procedures required. This incidence is due not only to the careful preoperative and postoperative care of these patients, but also to the selection and rejection of patients who have asthma and for whom some major surgical procedure has been proposed. The most common postoperative pulmonary complications encountered in this study were pneumonia, atelectasis and bronchitis.

## FISTULA BETWEEN THE ESOPHAGUS AND THE TRACHEOBRONCHIAL TREE

HERMAN J. MOERSCH AND WILLIAM S. TINNEY

ALTHOUGH the esophagus and the tracheobronchial tree are in close proximity one with the other and are frequently the site of serious disease, it is a comparatively rare occurrence for a direct communication to develop between the two. When such a communication or fistula occurs, it usually gives rise to an extremely distressing train of symptoms and frequently terminates fatally. However such a fistula may exist for many years and be compatible with a relatively comfortable existence.

Fistula between the esophagus and the tracheobronchial tree may be present at birth, and, when such is the case, is classified as congenital. Congenital fistula invariably manifests its presence with the first effort at deglutition. It is readily recognized and uniformly results in early death of the infant. In recent years, some progress has been made in surgical repair of such fistulas, but as yet this procedure remains a surgical triumph and has not become a routine method of treatment.

Fistulas that develop between the esophagus and the trachea and bronchi later in life are classified as acquired. Acquired fistula may be produced by variety of conditions. In our experience, acquired fistula is encountered more frequently than congenital fistula and offers a much more difficult diagnostic problem. It is the acquired fistula between the esophagus and the tracheobronchial tree that we wish especially to discuss.

### ANATOMY

A brief review of the anatomy of the mediastinum is essential to an understanding of the clinical features of esophagotracheobronchial fistula. The trachea, from its origin to its bifurcation, lies directly anterior to the esophagus. The two structures are in apposition except for occasional lymph nodes the most important of which are situated at the bifurcation of the trachea. At this level the esophagus curves slightly to the left and is crossed by the left main bronchus. The esophagus passes behind and to the right of the aortic arch, descending in the posterior mediastinum along the right side of the thoracic aorta. Lower in the mediastinum, as the aorta passes to the anterior aspect of the vertebral column the esophagus inclines anteriorly and to the left, passing in front of the aorta and to the left of it. Throughout its



course below the level of the fifth thoracic vertebra, the esophagus is in apposition with the posterior aspect of the pericardium. The esophagus passes through the diaphragm and joins the stomach at the level of the tenth thoracic vertebra. Ulcerating lesions of any of the foregoing structures may lead to the formation of fistulas. The commonest site of fistulas between the respiratory tract and the esophagus is at the bifurcation of the trachea or just above it. The left main bronchus is involved more frequently than the right.

### ETIOLOGY

Data on thirty-nine cases of acquired fistula between the esophagus and the tracheobronchial tree, encountered at the Clinic, were studied and the etiologic factors involved in production of the fistulas are listed in the accompanying table.

ETIOLOGIC FACTORS OF ESOPHAGO-TRACHEOBRONCHIAL FISTULA

Etiologic Factor	Cases	Per Cent
1 Carcinoma of esophagus	14	36
2 Trauma	5	13
3 Syphilis	4	10
4 Tuberculosis	4	10
5 Diverticulum of esophagus	2	5
6 Actinomycosis	1	
7 Carcinoma of thyroid	1	
8 Sarcoma of thyroid	1	
9 Carcinoma of trachea	1	
10 Carcinoma of bronchus	1	
11 Cause unknown	5	13
Total	39	

*Carcinoma* of the esophagus, as might be anticipated from a previous study by one of us,<sup>7</sup> was the most common cause for the fistula, being the etiologic factor in fourteen cases, or 36 per cent. The average age of this group was fifty-one years, the youngest patient being twenty-three years of age. Twelve of the patients were men and two were women, closely approximating the general incidence of carcinoma of

the esophagus as observed in the two sexes. The fistulous tract most frequently originated, as might be anticipated, from the middle third of the esophagus. This is explained by the fact that carcinoma of the upper third of the esophagus is comparatively rare, and the anatomic relation of the lower third of the esophagus does not predispose to the formation of fistulas. There is no correlation between the duration of the neoplasm in the esophagus and the formation of a fistula. It was also noted that the sinus tract does not always follow the most direct path but sometimes follows a devious and tortuous course. It is of interest that in two of the cases the carcinoma of the esophagus developed upon an old lye stricture. In four additional cases, a malignant lesion was a factor in the formation of the fistula although the neoplasm did not originate in the esophagus.

As shown in the table, there was one case respectively of carcinoma of the thyroid, sarcoma of the thyroid, carcinoma of the trachea and carcinoma of the bronchus in which the neoplasm was a factor in the formation of the fistula. If these four additional cases are added to the fourteen cases of carcinoma of the esophagus, there were eighteen cases, or 46 per cent in which the fistula was the result of a malignant lesion.

*Trauma*, in our experience, was the second most frequent cause for fistula between the esophagus and the tracheobronchial tree. In two instances the fistula occurred as the result of dilatation of a lye stricture, and in one of these cases the communication had been present for twenty-four years. Although lye stricture is not classified as an etiologic factor in the formation of esophagobronchial or esophago-tracheal fistula, still in four, or 10 per cent, of our cases a lye stricture was the primary lesion involving the esophagus and must be regarded as a contributory factor. Two of these cases are those mentioned in the previous paragraph in which carcinoma of the esophagus that had developed on an old lye stricture was the cause of the fistula. The third case of traumatic fistula was that of a carcinoma of the cardia of the stomach in which a fistula occurred following esophagoscopy. In the fourth case the fistula developed following an accident in which the patient was thrown violently against the steering wheel during an automobile accident. The esophagus was perforated and this injury resulted in the formation of a mediastinal abscess and erosion into the bronchus. Fatal hemoptysis occurred fourteen days after the injury. In the fifth case of traumatic fistula the lesion was caused by a gunshot wound in the neck with the formation of a fistula between trachea and the upper end of the esophagus which was successfully closed surgically.

*Syphilis* has been mentioned as a frequent cause of tracheo-esophageal fistula, although there are few specific references to cases in the literature. Gummatous infiltrations of the mediastinum may involve the esophagus and the respiratory tract secondarily, giving rise to the formation of a fistulous tract. Syphilitic aneurysms of the aorta occasionally erode into the esophagus and air passages and may lead to a similar result. Conner,<sup>3</sup> in 1903, studied data on 128 cases of syphilis of the trachea and bronchi, and found but two instances of perforation into the esophagus. In 1934, Bucher and Ono<sup>2</sup> and Lukens and Ono<sup>6</sup> were able to collect data on only twelve cases of esophagobronchial tracheal fistula of syphilitic origin.

We have had two cases in which we made a presumptive diagnosis of gumma of the mediastinum and two cases in which syphilitic aneurysm of the aorta resulted in the formation of fistulas. In all four cases the serologic reaction of the blood for syphilis was positive. One of the patients was of especial interest as he had been referred to the Clinic with a diagnosis of carcinoma of the bronchus and he indeed presented an excellent clinical and roentgenographic picture of such a disease. On bronchoscopic examination a large, fungating mass was found obstructing the left main bronchus. A specimen was removed from the tumor for microscopic diagnosis and was reported as containing inflammatory tissue and blood clots. Several days later the patient died as the result of a gastro-intestinal hemorrhage. At post-mortem examination it was discovered that the patient had an aortic aneurysm that had eroded into the bronchus, producing the large "tumor," and into the esophagus, leaving a direct fistulous tract between the esophagus and the left main bronchus.

The esophagus is relatively, but not absolutely, immune to *tuberculosis*. It may be involved by direct extension of tuberculous ulcers of the pharynx, by perforation of tuberculous abscesses of the vertebrae or, more commonly, by erosion of tuberculous tracheobronchial nodes into the esophagus. Flexner<sup>4</sup> reviewed this subject in 1893 and collected data on several cases in which the fistula was of tuberculous origin. Glynn<sup>5</sup> reported a case of tracheo-esophageal fistula caused by the erosion of tuberculous retrotracheal nodes. He also expressed the opinion that a fistula may start as a tuberculous ulcer in the trachea.

In four of our cases, tuberculosis was the underlying etiologic factor involved in the production of the fistula. In all instances the sputum was positive on examination for *Mycobacterium tuberculosis* and in one case the diagnosis was confirmed by postmortem examination. In all cases, the lesion probably resulted from the erosion of a tuberculous into the esophagus and the tracheobronchial tree. One patient had up a lung calculus six months after the fistula had developed.

Although tuberculosis is regarded generally as the underlying etiologic factor in the formation of traction diverticulum of the esophagus, this cannot always be proved. It is therefore advisable, for purposes of accuracy, to classify fistulas that develop between the esophagus and the tracheobronchial tree at the site of a traction diverticulum of the esophagus as distinct from those fistulas listed as being due to tuberculosis. In two of our cases, the fistula developed at the site of a traction diverticulum, and in one of these cases especially there was nothing to suggest that the diverticulum was due to tuberculosis. In the other case tuberculosis did seem to be a probable factor in the formation of the diverticulum, as demonstrated at postmortem examination.

In one case *actinomycosis* was the etiologic factor. This case has been reported previously by Vinson and Sutherland.<sup>9</sup> The patient lived for twenty years after the development of an esophagobronchial fistula. The diagnosis was established by the isolation of "sulfur bodies" from the sputum.

In five cases the cause underlying the development of the esophagobronchial fistula was not established definitely. In three of the five cases there was strong presumptive evidence that carcinoma of the esophagus was the cause of the difficulty, but inasmuch as positive microscopic examination of tissue from the lesion was lacking, these cases are classified as being of unknown cause. In the other two cases there does not exist any adequate explanation for the development of the fistula.

#### CLINICAL FEATURES

In contrast to the specific symptom complex of congenital esophago-tracheal fistula, the clinical picture of an acquired communication between these structures is variable and often indefinite. The clinical findings depend essentially on the primary pathologic changes and on the site and location of the sinus tract. For example, fistulas caused by the erosion of aortic aneurysms are usually terminal events and therefore are unsuspected before postmortem examination.

In most cases there is a certain sequence of symptoms which should arouse suspicion that an esophagotracheobronchial fistula exists. This is true particularly in cases of carcinoma of the esophagus and in those instances in which symptoms referable to the respiratory tract follow instrumentation of the esophagus. The patient usually has complained of dysphagia for a varying period before the onset of pulmonary symptoms. The presence of a communication between the esophagus and the tracheobronchial tree should be suspected when ingestion of food is followed by cough, expectoration and dyspnea. Solid food is swallowed fairly frequently without any difficulty and the first clue

may be an attack of strangling after taking liquids. This phenomenon is sometimes observed when the fistula is small. Occasionally, a small sinus tract becomes obstructed by solid foods and liquids can be swallowed without difficulty. In most instances there is a delay after deglutition before distress occurs. If the fistula is high, the paroxysm of choking is immediate and it may be almost impossible, from the history alone, to be certain that the patient does not have bulbar palsy. Ono and his associates<sup>2, 6</sup> observed that cough and expectoration are more likely to occur when the patient is on the left side, is upright or leans forward during deglutition than when he is in another position. This sign is explained by the fact that most fistulas arise in the anterior esophageal wall and are fairly frequently asymptomatic when the patient is in the recumbent position. Ono also elicited coarse rales in the sixth interspace in the paravertebral line after the patient had swallowed water.

Sometimes the lesion is discovered without having caused symptoms. Allen<sup>1</sup> reported two cases in which the fistulous tract was found during a routine roentgenoscopic examination of the gastro-intestinal tract with barium. The diagnosis was made in Myerson's<sup>3</sup> case as the result of the winding of swallowed thread around the parting wall between the trachea and the esophagus. In one of our cases, the presence of a communication between these structures was established prior to the patient's coming to the Clinic, when a stomach tube was passed into the esophagus and appeared in the bronchus. Because of extensive ulceration, esophagoscopy and bronchoscopy examination may fail to reveal the site of the fistula. Usually the lesion can be demonstrated most readily and safely by a roentgenoscopic examination after the patient has ingested iodized oil.

#### PROGNOSIS

The prognosis depends chiefly upon the primary lesion and upon the size of the sinus tract. A small fistula may be present for many years without causing much discomfort or any dangerous sequelae. However, the expectancy of life in most cases is short. This is clearly demonstrated by the fact that the cause of the fistula was a malignant lesion in almost half of our series. In the remaining group, death is usually the result of aspiration pneumonia, or of mediastinal or pulmonary abscesses. In rare instances fistulas have been known to close spontaneously.

Surgical measures may be of value in the treatment of esophago-bronchial fistula. They are especially of value in the treatment of fistulas due to trauma.

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# INTERSTITIAL CYSTITIS CLINICAL ASPECTS AND TREATMENT

THOMAS L. POOL

HUNNER<sup>8</sup> first described the syndrome of interstitial cystitis in 1914. Since that time various names have been used in an attempt to describe the lesion more accurately. Some of these names are elusive: ulcer, Hunner's ulcer, localized submucous fibrosis, panmural cystitis and paracystitis. At the Clinic we prefer the term "interstitial cystitis."

It is now thirty years since Hunner wrote of a rare type of ulcer of the bladder occurring in women. Knowledge has increased to the extent that it is known that the lesion is not confined to the female sex and that it is rarely an ulcerated lesion. Hunner called attention to the fact that the lesion was on the mobile portion of the bladder, that the lesion was easily overlooked and that the urine was frequently normal. He noted also that many surgical procedures had been performed on women suffering from interstitial cystitis. Likewise, he reported that the cystoscopic findings were not always characteristic.

Emmett<sup>5</sup> has stated that interstitial cystitis probably remains undiagnosed more often than any other lesion affecting the urinary tract. Beyond doubt it is one of the least understood lesions.

## ETIOLOGY

The etiology of interstitial cystitis is obscure. Most observers have stressed the theory of focal infection. Meisser and Bumpus<sup>10</sup> thought that interstitial cystitis might be due to focal infection and were able to reproduce the lesion in thirteen of nineteen rabbits by injecting green-producing streptococci isolated from the teeth of patients suffering from interstitial cystitis. Some authors, including Hunner, have attributed the lesion to a previous infection in the mouth or throat. It is doubtful if all the cases can be explained on this basis. It is interesting to note that Fister has pointed out the similarity in the etiology, pathology and symptomatology of interstitial cystitis and lupus erythematosus.

Occasionally statements have been made that all those who suffer from interstitial cystitis have had previous bouts of nonspecific infection of the urinary tract. The authors who make these statements are of the opinion that the lesions produced are the result of the infection is purely a matter of speculation.

Engel<sup>6</sup> felt that interstitial cystitis could be produced by impaired circulation caused either by vascular disease or by some form of nutritional deficiency. Others have stated that the lesions are the result of an embolic process.

A hormonal basis for interstitial cystitis has been advocated often. This has to be considered in view of the fact that most women are afflicted during the age of approaching menopause or beyond the climacteric. Also women frequently complain that their symptoms are worse just prior to or during the menstrual period. These symptoms, however, might be explained by other means than a relationship between the lesion of interstitial cystitis and the glands of internal secretion and furthermore, many patients who do not have evidence of hormonal imbalance suffer from interstitial cystitis. It is difficult to explain the occurrence of the disease in men on this basis.

#### PATHOLOGY

Broders<sup>2</sup> expressed the opinion that the process is an inflammation of the connective tissue of the bladder and that it is most pronounced and apparently primary, in the subepithelial connective tissue. The layer of subepithelial connective tissue which consists of the connective tissue of the mucosa and the so-called submucosa, lies between the epithelium and the musculature. The inflammatory process extends to the epithelium, intermuscular connective tissue, musculature and serosa.

When tissue involved by the lesion is removed and examined, the inflammation is found to be chronic, however, it would be contrary to sound reasoning to assume that the inflammation is chronic from the outset. It seems reasonable to assume, therefore, that the inflammatory process passes through acute, subacute and chronic phases and there are exacerbations of acute and subacute phases which tend to intensify the chronic phase. These various phases seem to be borne out by clinical observations.



erous erythrocytes within and outside of the blood vessels and blood spaces and varying degrees of edema. In other words, the process is comparable to that found in the inflammatory granulating base of a chronic excavated ulcer of the urinary bladder or stomach.

The inflammatory process in the intermuscular connective tissue, musculature and serosa is less pronounced than that in the subepithelial connective tissue. The serosa is usually thickened. The musculature may be distorted to some extent, however, there is little loss of continuity of the musculature, in contrast to the marked loss of continuity found in an excavated ulcer of the bladder or stomach.

In some cases fibrous connective tissue is increased little whereas in others the increase is so marked that real fibrosis is produced throughout the vesical wall with or without hyaline degeneration. The amount of fibrosis is probably in direct proportion to the duration of the inflammatory process. The process as a whole resembles closely that relatively rare lesion of the stomach known as "linitis plastica of non-neoplastic type."

#### SYMPTOMS AND CLINICAL FEATURES

Interstitial cystitis is essentially a chronic disease. Most of the patients when first seen give a history of a long duration of symptoms. Many state that they have had symptoms for a time and then the symptoms have disappeared only to recur more severely than before. These patients are frequently chronic invalids and, although they are not confined to bed, they are more or less incapacitated and are confined to their homes because of the frequency of urination. Usually women patients state that they are no longer able to do their housework because of the pain. Often they are no longer able to have sexual intercourse because of the pain and divorce is not uncommon in these cases. The symptoms are at times bizarre.

*Frequency of micturition*, both during the day and night, is the most common symptom. A patient who does not complain of nocturia rarely has interstitial cystitis. Early in the course of the disease this frequency is probably on a basis of irritation from the lesion. Later, however, the capacity of the bladder has been so reduced that this frequency is mechanical in nature.

*Pain* also is a common symptom. It usually is produced by distention of the bladder, it is relieved by micturition but recurs when the bladder becomes distended again. This pain may be situated in the vagina, perineum or vulva, but is usually suprapubic and the patient frequently will point to the exact site of the discomfort. The pain varies from moderate discomfort to extreme, excruciating pain which will not

allow the patient any rest. Bending or stooping aggravates the pain as does any form of exercise. Even walking at times will cause so much discomfort that this mild form of exercise must be discontinued.

Occasionally *hematuria* may be stated to be one of the symptoms of interstitial cystitis. Most of the textbooks give this as a common symptom. It is rare in my experience. *Dysuria*, difficulty in voiding, backache, and so forth likewise are rarely seen but are usually described as symptoms of this disease.

It should be pointed out that patients who have this disease often are considered neurotic. Many wander from physician to physician. They receive various forms of treatment and are subjected to almost all the known surgical procedures. The nervousness they manifest frequently disappears as the symptoms are alleviated after the correct diagnosis has been made and the correct form of treatment has been instituted.

The physical examination reveals no typical findings. Often the patient is nervous and apprehensive, and at first glance may appear to be so-called "neurotic." Laboratory findings are frequently entirely negative. The urine usually contains few if any pus corpuscles. Grim's stain and bacterial culture of the urine usually do not disclose bacteria.

Interstitial cystitis is usually a disease of adult life but may occur in patients who are still in their teens. It is much more common among women than among men. My impression, although it may be erroneous, is that Negroes rarely have the disease.

#### DIAGNOSIS

The diagnosis is made on the history, urinary findings and the findings on cystoscopic examinations which may have to be repeated a number of times before the correct diagnosis is established. It is not uncommon to perform cystoscopic examination in a case in which interstitial cystitis is thought present only to find normal appearing mucosa. However, re-examination of the bladder at a later date may reveal the lesion. Hence the term 'elusive' applies to this disease.

Cystoscopic examination reveals that the bladder is rather irritable and that the capacity is small. There are exceptions to these observations but it is rare to find interstitial cystitis when the vesical capacity is normal. The appearance of the lesion is not characteristic and tends to change greatly from time to time. The color is usually described as salmon pink. Single or multiple lesions may be present. Regions of inflammation are surrounded by enlarged blood vessels. Punctate lesions are present occasionally but true ulceration as seen through the cystoscope is rarely observed. When ulceration does occur it is prol

due to some secondary factor and further diagnostic procedures should be carried out before the diagnosis of interstitial cystitis is established. For this reason I feel that the term "Hunner's ulcer" is undesirable. The pain can be reproduced by touching the lesion with the beak of the cystoscope or by overdistention with irrigating fluid.

One of the most characteristic features of this disease is that bleeding is produced by the slightest overdistention of the bladder. Severe scarring occurs occasionally in cases in which the disease has been present for a long time. When the disease is far advanced the capacity of the bladder is small and frequently nothing can be seen on cystoscopic examination to suggest a lesion of interstitial cystitis. In such cases the diagnosis may have to be made by inference. When cystoscopic examination is performed under anesthesia, as is frequently required, care must be taken since a marked splitting of the mucosa or even rupture of the bladder may occur if too much irrigating fluid is placed in the bladder. Following treatment with silver nitrate, the vessels are usually distended to a marked degree.

In the differential diagnosis, of course, tuberculosis must be excluded in all cases. At times this may be difficult without the aid of inoculation of guinea-pigs. Other inflammatory lesions of the bladder and urethra must be considered since more than one type of disease may be present. Occasionally, interstitial cystitis may exist as well as benign prostatic enlargement. Removal of the prostatic tissue does not relieve these patients of their symptoms.

#### TREATMENT

Various forms of treatment have been advocated but none has proved to be entirely satisfactory. Dodson<sup>4</sup> in 1926 advocated the use of solutions of silver nitrate in increasing strengths as the treatment of choice. As early as 1855, Mercier<sup>11</sup> reported that in some cases excellent results were obtained by the use of silver nitrate in the bladder. From his description, it seems likely that many of the patients whom he treated were suffering from interstitial cystitis.

Nelson and Pinard<sup>12</sup> obtained satisfactory results by using silver nitrate as recommended by Dodson. Folsom and his co-workers<sup>7</sup> advocated subtotal cystectomy as a result of experimental work on dogs in which regeneration of the bladder occurred after subtotal cystectomy had been performed. Deep roentgen therapy<sup>9</sup> has been tried but is not especially beneficial. Various strengths<sup>14</sup> of phenol have been applied directly to the lesion by different investigators. Alexander and Christie<sup>1</sup> suggested the submucous injection of alcohol about the lesion. <sup>13</sup> reported on the use of aniline dyes in sixteen cases. He used

methyl violet, gentian violet and crystal violet in various concentrations and in all but one case improvement was noted

Of all forms of treatment advocated, the one most commonly used probably has been overdilatation of the bladder under anesthesia. Fulguration of the lesion is performed occasionally at the same time. Many other forms of therapy have been tried but have been discarded.

**Silver Nitrate**—In 1941 Crenshaw and I<sup>12</sup> made a preliminary report on the use of solutions of silver nitrate of increasing concentrations in thirty-four cases of interstitial cystitis observed at the Mayo Clinic. The treatment is carried out as follows: A urethral catheter is inserted and the contents of the bladder are evacuated. The bladder then is irrigated with a saturated solution of boric acid. Following the irrigation, 30 to 60 cc. of a 1:5,000 solution of silver nitrate is instilled into the bladder and permitted to remain there for three or four minutes if it does not cause intolerable irritation. At the end of this period the solution is permitted to run out through the catheter which is then withdrawn. The patient usually experiences some dysuria and vesical irritability for two or three hours.

Treatments are repeated daily unless severe reactions occur, in which case they are repeated every other day. At subsequent treatments, the concentration of silver nitrate in the solution is increased to 1:2,500, 1:1,000, 1:750, 1:500, 1:400, 1:200 and finally 1:100. If at any time the reaction is too severe, the concentration is increased more slowly.

The results of this form of treatment will be discussed in the section on prognosis. It is safe to say that this form of treatment is as good if not better than any that has been tried at the Clinic. It is impossible to predict which patient will gain relief from symptoms and which one will not. Frequently a second or even a third course of treatment may be necessary when the first course was not effective. In those cases in which a good result is not obtained, overdilatation under anesthesia will often give relief of symptoms for a time. Many physicians are advocating continuous irrigations and gradually increasing the strength of the solution of silver nitrate in much the same manner which I have described. Others suggest irrigations with silver nitrate by means of a tidal drainage apparatus. This has not been tried at the Clinic but should be a good method to employ.

#### PROGNOSIS

No one has been able to follow a large series of patients long enough to warrant a dogmatic statement concerning the number of these patients who will get well. It is also impossible at this time to say how

often spontaneous cures may occur. Patients may suddenly be relieved of their symptoms without any treatment or after inadequate treatment. Also, the lesion in the bladder may suddenly disappear before adequate treatment has been carried out. While no definite figures on cure can be given, the prognosis seems much better than was thought formerly.

In a recent report from this clinic the results obtained in the use of silver nitrate therapy were given. The immediate results of treatment were excellent or good in sixty-six (89 per cent) and poor in eight (11 per cent) cases. In eight cases in which results of treatment with silver nitrate were poor, subsequent overdistention of the bladder produced relief of the symptoms. Follow-up data were obtained in seventy of the seventy-four cases. In twenty-two (31 per cent) of the seventy cases, symptoms did not recur after a single course of treatment with silver nitrate. Of course, enough time has not elapsed for us to draw definite conclusions but these patients were all treated prior to December 31, 1942. It may be that some or all of these patients may have received permanent relief. Time only will tell the percentage of cure. At any rate, the condition of most patients suffering from interstitial cystitis can be improved or their symptoms can be relieved to some extent. It is only in the rare case that extensive surgery is required in order to produce relief.

#### SUMMARY AND CONCLUSIONS

Interstitial cystitis is a poorly understood urologic entity which often is not recognized. Its manifestations are frequently bizarre, and patients who have the disease may be classified as neurotics.

Treatment with silver nitrate is as satisfactory as, or more satisfactory than, any other type of treatment that has been employed at the Clinic. It is economical and convenient, and does not require the use of anesthesia. So far as I have been able to determine, there are no contraindications to this type of treatment. It can be carried out easily by the general practitioner and will enable him to co-operate with the urologist in the treatment of this disease. In cases in which the bladder is extremely irritable it may be necessary to employ overdistention of the bladder before starting treatment with silver nitrate.

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## CONTRIBUTORS TO THIS NUMBER

Donald G. Anderson, M.D., Instructor in Medicine, Boston University School of Medicine, Research Fellow in Medicine, Evans Memorial, Massachusetts Memorial Hospitals

David Ayman, M.D., Instructor in Medicine, Tufts Medical School, Associate Visiting Physician, Beth Israel Hospital

Stewart H. Clifford, M.D., Instructor in Pediatrics and Child Hygiene, Harvard Medical School, Associate Visiting Physician, The Infants' and Children's Hospitals of Boston, Pediatrician, Boston Lying-in Hospital.

Stanley Cobb, M.D., Bullard Professor of Neuropathology, Harvard Medical School, Psychiatrist-in-Chief, Massachusetts General Hospital

Louis K. Diamond, M.D., Assistant Professor of Pediatrics, Harvard Medical School, Visiting Physician, Children's Hospital, Visiting Physician, Infants' Hospital

Edward S. Emery, Jr., M.D., Senior Associate in Medicine, Peter Bent Brigham Hospital, Instructor in Medicine, Harvard Medical School

Charles F. Ferguson, M.D., Assistant in Otorhology, Harvard Medical School, Associate Visiting Otolaryngologist, The Infants' and Children's Hospitals of Boston

Maxwell Finland, M.D., F.A.C.P., Assistant Professor of Medicine, Harvard Medical School, Chief, Fourth Medical Service and Associate Physician, Thorndike Memorial Laboratory, Boston City Hospital

Chester M. Jones, M.D., F.A.C.P., Clinical Professor of Medicine, Harvard Medical School, Physician, Massachusetts General Hospital

Elliott P. Joslin, M.D., Sc.D., F.A.C.P., Clinical Professor of Medicine Emeritus, Harvard Medical School, Medical Director, George I. Baker Clinic, New England Deaconess Hospital, Consulting Physician, Boston City Hospital

Chester S. Keefer, M.D., F.A.C.P., Wade Professor of Medicine, Boston University School of Medicine, Director, Evans Memorial, and Physician-in-Chief, Massachusetts Memorial Hospitals, Chairman, Committee on Chemotherapeutics and Other Agents, Division of Medical Sciences, National Research Council



## CONTRIBUTORS TO THIS NUMBER

Edward B D Neuhauser, M D , Instructor in Roentgenology, Harvard Medical School, Roentgenologist, The Infants' and Children's Hospitals of Boston, Roentgenologist, Boston Lying-in Hospital

Edward L Pratt, M D , Assistant in Pediatrics, Harvard Medical School, Junior Attending Physician, Infants' Hospital, Junior Attending Physician, Children's Hospital

Francis M Rackemann, M D , F A C P , Lecturer in Medicine, Harvard Medical School, Physician, Massachusetts General Hospital

Edward C Reifenstein, Jr , M D , F A C P , Research Fellow in Medicine, Harvard Medical School, Instructor in Medicine and Psychiatry, Syracuse University College of Medicine (on leave), Graduate Assistant in Medicine, Massachusetts General Hospital

John Rock, M D , Visiting Surgeon and Director of Fertility, Endocrine and Rhythm Clinics, Free Hospital for Women, Brookline, Massachusetts, Research Associate in Obstetrics and in Gynecology, Harvard Medical School

Bernardo A Samper, M D , Research Fellow, Thorndike Memorial Laboratory and Harvard Medical School (Residence Bogota, Colombia )

George W Thorn, M D , F A C P , Hersey Professor of the Theory and Practice of Physic, Harvard Medical School, Physician-in-Chief, Peter Bent Brigham Hospital

Frank H Tyler, M D , Research Fellow in Medicine, Harvard Medical School, Resident Physician, Peter Bent Brigham Hospital

Francis L Welle, M D , Assistant in Laryngology, Harvard Medical School, Associate Surgeon, Massachusetts Eye and Ear Infirmary and Massachusetts General Hospital

Paul D White, M D , F A C P , Physician, Massachusetts General Hospital, Lecturer in Medicine, Harvard Medical School

Robert H Williams, M D , Associate in Medicine, Harvard Medical School, Assistant Physician, Thorndike Memorial Laboratory, Junior Visiting Physician, Boston City Hospital

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By Dr Edward C Reifenstein

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# THE MEDICAL CLINICS of NORTH AMERICA

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*Symposium on Specific Methods of Treatment*

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## THE TREATMENT OF STAPHYLOCOCCIC INFECTIONS WITH PENICILLIN

DONALD G. ANDERSON, M.D.\* AND CHESTER S. KEEFER, M.D., F.A.C.P.†

RECENT years have seen a marked increase in the attention directed to the problem of staphylococcic infections. Much of this interest has grown out of a fuller realization of the frequency with which the staphylococcus is encountered either as the primary infecting agent or as an important secondary invader. Medical thought has been further stimulated by the awareness that whereas infections caused by other pyogenic bacteria respond well to the sulfonamides, staphylococcic infections do not, and therefore still present a serious therapeutic problem.

It was natural, therefore, that confirmation of Florey's early observations on the effectiveness of penicillin in staphylococcic infections should be eagerly awaited. Today a sound body of clinical experience

---

From the Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine. The penicillin was provided by the Office of Scientific Research and Development from supplies assigned by the Committee on Medical Research for clinical investigations recommended by the Committee on Chemotherapeutics and Other Agents of the National Research Council.

\* Instructor in Medicine, Boston University School of Medicine and Research Fellow in Medicine, the Evans Memorial, Massachusetts Memorial Hospitals.

† Wade Professor of Medicine, Boston University School of Medicine, Director, Robert Dawson Evans Memorial, and Physician in Chief, Massachusetts Memorial Hospitals, Chairman, Committee on Chemotherapeutics and Other Agents, Division of Medical Sciences, National Research Council.

has accumulated that clearly demonstrates that penicillin is the most effective agent yet discovered for the treatment of staphylococcic infections. This statement is well substantiated by the fact that in staphylococcic bacteremia penicillin has lowered the mortality rate from 85 to 20 per cent, and that in serious staphylococcic infections without bacteremia it has effected recovery or improvement in more than 80 per cent of cases.

In today's clinic we shall present a group of cases that illustrate clearly the manner in which the problem of staphylococcic infections has been met by penicillin. Before presenting these cases, however, we shall review briefly some of the more important general considerations that must be heeded in penicillin therapy.

### GENERAL CONSIDERATIONS

At the outset it should be emphasized that to obtain a maximal therapeutic effect with penicillin, one must be acquainted with its pharmacologic properties. There is not time this morning to do more than summarize the studies that have been carried out on the absorption, excretion and distribution of penicillin. This work is reported fully in other papers.

It has been clearly shown that the enteral administration of penicillin is not effective and that, if adequate absorption is to be obtained, the drug must be given by intramuscular or intravenous injection. Because penicillin is rapidly excreted in the urine, an effective concentration of the drug can be maintained in the body during treatment only if the injections are repeated at intervals not exceeding 3 to 4 hours throughout the day and night. The use of a constant intravenous drip is also an effective method of achieving the same result.

Penicillin does not pass from the blood into the subarachnoid space or into the various serous spaces of the body in significant concentrations, so that it is essential in treating infections of the meninges, of the body cavities, or of the joints to inject the drug directly into the infected cavity. It is absorbed slowly from these sites, and it need be injected only once or, at the most, twice in each 24-hour-period.

With regard to the action of penicillin, it seems clear that its action *in vivo* is bacteriostatic rather than bactericidal. It prevents the growth and multiplication of the infecting organisms, but the actual killing of the bacteria is accomplished by the phagocytic cells of the host. It can thus be seen that it is necessary to continue treatment with penicillin until the infection has been definitely controlled or eradicated. Experience has shown that the staphylococcus dies hard even when it is attacked by as potent an agent as penicillin. Prolonged and intensive therapy is therefore usually necessary, and relapses are frequently encountered when the drug is discontinued too soon after the first signs of improvement have appeared.

## STAPHYLOCOCCIC BACTEREMIA

We have selected for presentation this morning 3 cases of staphylococcic bacteremia. It will be seen that each case presents its own peculiar problem.

**Staphylococcic Pneumonia with Bacteremia**—More and more recognition is being given to the important role that the staphylococcus occupies in respiratory infections in infants and very young children. Frequently it is the cause of a fulminating pneumonia that rapidly causes death or results in a serious complication such as empyema, lung abscess, or pericarditis.

**CASE I—M. C.**, a 2-year-old girl, had a sudden chill 3 days before entry to the hospital. The family physician found the temperature to be 105° F and heard

## HEMOLYTIC STAPH. AUREUS BACTEREMIA &amp; PNEUMONIA

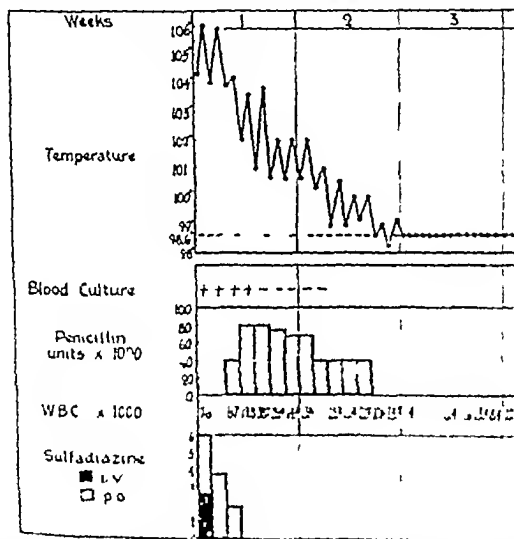


Fig. 76 (Case I)—Clinical course in a 2-year-old child with *Staphylococcus aureus* pneumonia and bacteremia that did not respond to intensive sulfadiazine therapy. Complete recovery followed the use of penicillin. The dosage of penicillin given during the first 6 days was large for a patient of this age. The patient received a total of 535 (60) units of penicillin intravenously over a period of 9 days.

After the first 9 days, 4 and one-half grams of sulfadiazine was given during the next 3 days without improvement, and the patient was then taken to the hospital. The course of the illness after admission is shown in Fig.

On admission the patient was desperately ill, with rapid grunting respirations. The temperature was 105.8° F. Signs of consolidation were present over the right lower lobe, and x-ray examination of the chest showed a diffuse bronchopneumonic process. During the first day 2.5 gm of sodium sulfadiazine was given intravenously and 3.5 gm by mouth. On the second day another 3.5 gm was given by mouth, and on the third day 1.75 gm had been given orally when the blood culture taken on entry was reported as positive for *Staphylococcus aureus*. Blood cultures taken on the second and third days were subsequently also found to be positive for the same organism. When the positive blood culture was reported, penicillin therapy was begun.

During the first 3 days 10,000 units of penicillin was given intramuscularly every 3 hours day and night, and at the end of this period the patient was greatly improved. The blood culture taken 24 hours after the administration of penicillin was still positive, but all blood cultures taken thereafter were negative. Although the temperature was 103.8° F on the evening of the third day, the patient no longer appeared toxic and was taking an interest in her surroundings. Since the critical stage of the illness had apparently passed, the dosage of penicillin was reduced to 7500 units. Seventy-two hours later, when the temperature was almost normal and recovery seemed assured, it was further decreased to 5000 units. Treatment was continued for another 4 days at this dosage and was then stopped. At this point the patient appeared entirely well and an x-ray film of the chest showed the pneumonic process to have almost completely cleared.

In summary, this patient had staphylococcic pneumonia with bacteremia that was not influenced by 4 days of intensive sulfonamide therapy. Following the administration of 535,000 units of penicillin over a period of 9 days, complete recovery resulted.

What we attempted to do in this case, as in all cases of staphylococcic bacteremia, was to bring the infection under control rapidly and to clear the blood stream of bacteria as soon as possible. To accomplish this aim, large doses of penicillin were given during the first few days. The dosage was gradually reduced as improvement appeared, but treatment was continued until the infection had been completely eradicated. It is noteworthy that even with large doses of penicillin the blood culture did not become negative until after 48 hours of therapy.

Attention should be drawn to the fact that the patient showed striking clinical improvement at a time when the temperature was still markedly elevated. It has been noted by many observers that in serious staphylococcic infections treated with penicillin, improvement in the general condition is frequently a more reliable guide than is the temperature chart for assessing progress during the first few days of treatment.

**Acute Hematogenous Osteomyelitis with Staphylococcic Bacteremia**  
—This not uncommon disease formerly ended fatally in about 25 per cent of cases and usually caused prolonged disability in those patients who survived the acute illness. The following case illustrates the improved outlook that may be expected in this disease from the use of penicillin.

CASE 11—J. D., a 10-year-old girl, developed a blister on the right heel 7 days before entry to the Massachusetts Memorial Hospital. The blister became infected. Two days before entry she developed a temperature of 103° F., and the next day she complained of severe pain in the lower end of the right femur. On the day of entry the temperature rose to 106° F. and the patient became delirious.

Physical examination showed a well-developed young girl who was acutely ill. The right thigh was slightly swollen and there was exquisite tenderness over the lateral aspect of the lower end of the right femur. There was marked pain on flexion of the right knee, which contained a small amount of fluid. An infected blister 1.5 cm. in diameter was present over the right Achilles tendon.

## ACUTE OSTEOMYELITIS WITH STAPHYLOCOCCUS AUREUS BACTEREMIA

J. D. ♀ Age 10 years

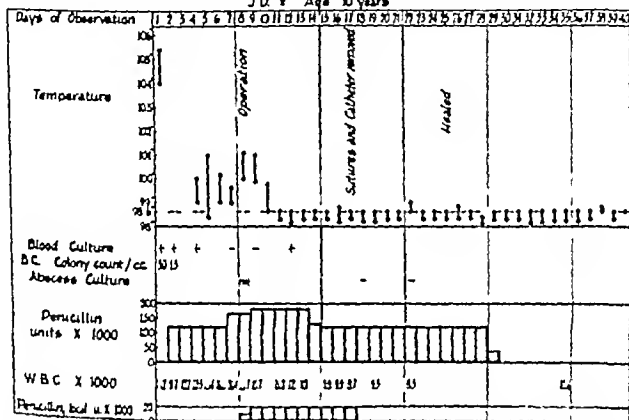


Fig 77 (Case 11)—Clinical course of a case of acute osteomyelitis of the femur with *Staphylococcus aureus* bacteremia. After initial improvement temperature and white cell count began to rise on the fifth day. Operation was performed on eighth day with the evacuation of a large soft tissue abscess and the release of pus under pressure from the medullary cavity. Recovery thereafter was uneventful. Patient received a total of 2,760,000 units of penicillin intramuscularly over a period of 28 days, and 190,000 units locally over a period of 10 days.

Blood culture on entry showed 32 colonies of *Staphylococcus aureus* per cubic centimeter. X-ray examination of the femur showed no abnormality. Figure 77 shows the course of the illness.

A clinical diagnosis of acute hematogenous osteomyelitis of the right femur was made at the time of admission and penicillin therapy was immediately instituted. For the first 5 days 15,000 units of the drug was given intramuscularly every 3 hours. After 48 hours of treatment the temperature was normal and patient appeared quite comfortable. Twenty-four hours later the temperature began to rise as did the white cell count. At the same time the swelling of the right thigh was detectable for the first time. The swelling was even more pronounced as the patient became more and more ill. The dose of penicillin was increased to 30,000 units but after another 48 hours when this failed to effect a cure, the patient was taken to the operating room for a radical debridement of the femur.



This case has been presented to bring out an important fact, namely, that even massive doses of penicillin will not save a patient who is moribund. Penicillin is a potent bacteriostatic agent, but for it to effect recovery its action must be supplemented by the workings of the normal defense mechanisms of the body.

In addition to being ineffective in patients who are moribund, penicillin occasionally fails to bring about recovery in cases of staphylo-

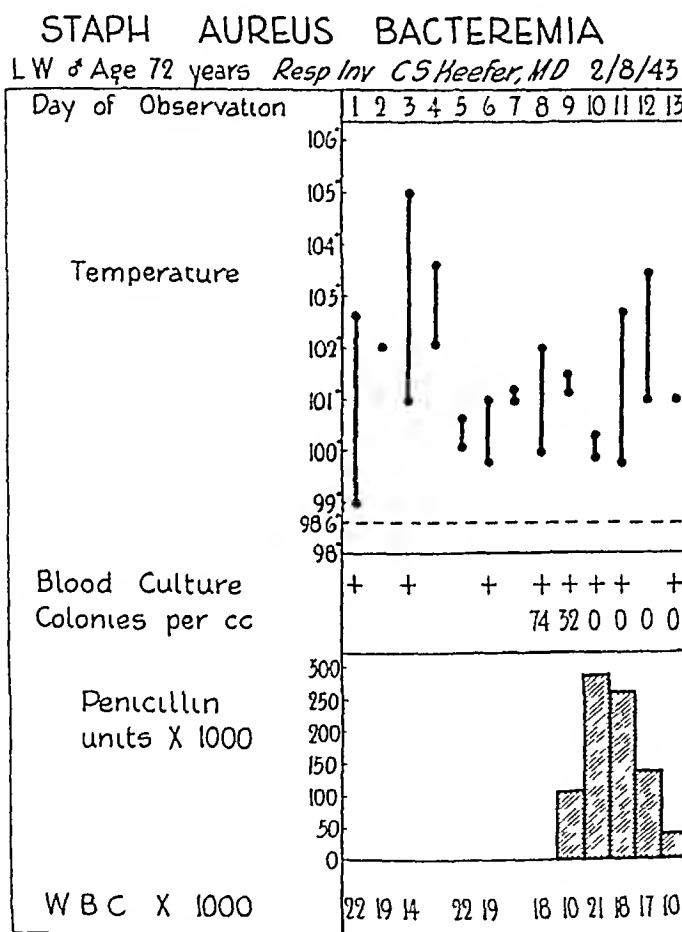


Fig 78 (Case III) —This chart shows the failure of massive doses of penicillin to clear the blood stream or prevent death in a patient with *Staphylococcus aureus* bacteremia who was moribund at the time treatment with penicillin was started. Total penicillin dosage was 915,000 units given over a period of 5 days.

coccic bacteremia for other reasons. Failures have occurred in patients who have been inadequately treated, in those who had an established bacterial endocarditis at the time treatment was begun, in those in whom the infection has become localized in areas inaccessible to surgical drainage, in those whose organisms have become resistant to penicillin, and, of course, in those who have had other serious associated diseases.

## LOCALIZED STAPHYLOCOCCIC INFECTIONS

We shall now turn to a discussion of the use of penicillin in localized staphylococcic infections. Two cases that illustrate some of the problems presented by infections of this type will be considered in detail.

In discussing localized staphylococcic infections, it is important to separate cases in which the infection is acute from those in which it is chronic or recurrent. The management of therapy and the results obtained may differ considerably depending on which type of lesion confronts one.

In acute infections, particularly when treated early, the impairment of blood supply is frequently minimal and penicillin diffusing from the blood gains ready access to the infecting organisms. In addition, the destruction of tissue may be relatively slight so that resolution and repair can proceed rapidly. When the infection is chronic, on the other hand, poorly vascularized dense fibrous tissue surrounding the lesion may prevent the diffusion from the blood of penicillin in adequate concentrations. Furthermore, encysted viable bacteria may persist in such tissue and later serve as a focus for the reactivation of the infection. Finally, repair and healing may be greatly delayed.

Our aim in treating acute infections without bacteremia is much the same as the one that we have before us in treating cases of staphylococcic bacteremia. In each case the objective is to bring the infection under control as rapidly as possible, and then to continue treatment until recovery is complete. To accomplish this result large doses of penicillin are frequently necessary during the first few days of treatment. Once the infection is controlled, the dosage can often be reduced with safety.

In the treatment of chronic infections our efforts are directed toward sterilizing the lesion and keeping it sterile until repair and healing have taken place. In such cases since healing may be slow and since the infection is frequently already more or less localized emphasis is more properly placed on the duration than on the intensity of treatment.

**Furuncle of the Nose with Cellulitis of the Face**—The following case is an example of a potentially serious acute localized staphylococcic infection treated successfully with penicillin.

**Case IV**—E. G., a 56-year-old man, developed a small furuncle on the left nostril 8 days before he entered the hospital. During it was progressive swelling first of the nose and then of the soft left side of the face. Twenty-four hours before entry both nostrils were markedly edematous and the patient had difficulty in opening his mouth. Swelling was intensely painful. The patient had had no chills or fever, but he did complain of mild feverishness and malaise. Physical examination revealed a purulent discharge from the left nostril. The nose was very red and swollen to about twice its normal size. In the vestibule of the left nostril there was a small discharging sinus. The soft tissue of the left side of the face were markedly swollen.

indurated Both eyes were edematous and could be opened only with great difficulty There was no proptosis, and the external ocular movements were normal

Laboratory studies showed the white cell count to be 20,000, with 85 per cent polymorphonuclear leukocytes A blood culture was sterile Culture of the furuncle showed *Staphylococcus aureus*

Immediately after entry the patient was started on penicillin, receiving 15,000 units intramuscularly every 2 hours for the first 3 days The dosage was then reduced to 15,000 units every 3 hours, and this dosage was continued for the next 7 days After 24 hours of treatment there was a marked decrease in the edema of the eyes and face Improvement was progressive, and by the fourth day the eyes and the tissues of the left cheek had resumed their normal appearance The nose was still extremely swollen At this time the patient stated that he felt entirely well

The swelling of the nose gradually receded On the eighth day a small superficial abscess ruptured through the skin on the left side of the nose During the next 48 hours there was a rapid resolution of the swelling, so that on the tenth day, when penicillin was discontinued, the only residual signs were a very small amount of redness and edema at the extreme tip of the nose Three days later the nose appeared entirely normal

This patient received a total of 1,200,000 units of penicillin over a period of 10 days The case demonstrates clearly how an acute, rapidly spreading and potentially dangerous localized staphylococcic infection was quickly controlled and finally eradicated by the administration of penicillin The blood supply to the infected area was unimpaired and tissue destruction was minimal

**Chronic Osteomyelitis of the Femur**—The last case to be presented is an example of an extremely common form of chronic localized staphylococcic infection

**CASE V**—M G, a 44-year-old woman, developed acute osteomyelitis of the right femur at the age of 12 Following incision and drainage a sinus formed This continued to drain for 9 years and then healed after sequestrectomy was performed For 22 years the patient had no further symptoms until 1 year before entry, when a new abscess developed and drained spontaneously A sinus formed and continued to drain 5 to 10 cc of pus daily until entry Except for a tendency to easy fatigue, the patient had no constitutional symptoms

Physical examination showed the patient to be well nourished and well developed She did not appear ill Positive findings were confined to the right thigh Six centimeters above the right knee on the medial aspect of the thigh was a small discharging sinus 0.5 cm in diameter This sinus led to the femur The tissues about the sinus were fibrotic but showed none of the signs of acute inflammation

Laboratory studies showed both the red cell and the white cell count to be normal Culture of the sinus was positive for *Staphylococcus aureus* X-ray examination of the right femur showed the distal two fifths of the shaft to be thickened and sclerosed Near the distal end of the shaft was a small cavity No definite sequestra could be demonstrated The patient's course is shown in Figure 79

The patient was given 10,000 units of penicillin intramuscularly every 3 hours for 16 days The 3 A.M. dose was omitted during the first 10 days of treatment but was given regularly for the last 6 days During the first week the daily drainage which had amounted to 5 to 10 cc on entry, was reduced to 1 to 2 cc After 9 days, cultures of the sinus were sterile and drainage consisted of only a few drops of clear serous fluid On the last day of treatment the sinus was completely

dry, and 4 days later, or 20 days after the beginning of treatment, it was completely epithelialized

A total of 1,120,000 units of penicillin was given over a period of 16 days.

### CHRONIC OSTEOMYELITIS OF THE FEMUR

M G ? Age 44 years

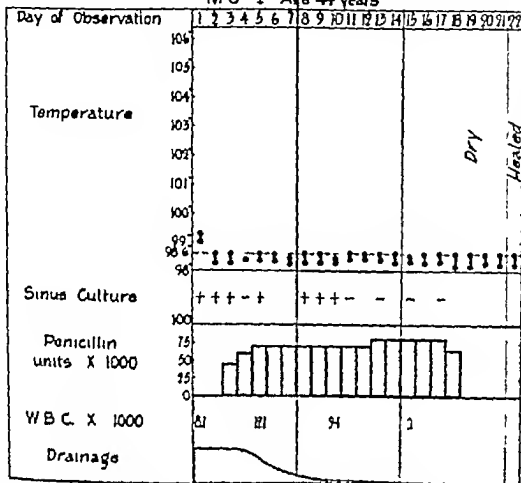


Fig 79 (Case V) - Clinical course in a patient with chronic osteomyelitis treated with penicillin. The chart shows the marked reduction in drainage that occurred during first week of therapy. Cultures of the sinus became sterile after 8 days of treatment and the sinus healed 20 days after the beginning of treatment. The patient has been followed for 1 year and has had no recurrence. A total of 11,000 units of penicillin was given over a period of 16 days.

This patient has been followed for 1 year and there has been no recurrence of drainage.

Chronic osteomyelitis is the commonest important chronic localized staphylococcic infection with which one has to deal. Clinical experience has shown that almost all patients are benefited by penicillin and that in about 75 per cent of cases temporary arrest of the disease with healing of all sinuses can be obtained. Not all patients, however, respond as quickly as did this one and it is frequently necessary to continue treatment for 3 to 4 weeks and occasionally for longer periods. This patient received a maximum dose of 80,000 units a day. In many cases the dosage must be increased to 120,000 - 160,000 units a day before progress is noted. The presence of sequestra has a direct bearing on

treatment and on the results. If they are present and are not removed, healing frequently fails to take place. If it takes place, relapses are extremely prone to occur. When we first began to use penicillin, several of our cases ended in failure because sequestra were not removed. More recently Dr. Louis G. Howard has removed the sequestra in every case in which they could be demonstrated by x-ray. In such cases sequestrectomy is usually preceded by intramuscular penicillin therapy for 4 to 5 days. The incision is closed, and postoperatively penicillin is administered both intramuscularly and locally by the method described in Case II.

Occasionally relapses have occurred in patients in whom no sequestra could be demonstrated. These patients are usually found to have extensive fibrosis of the soft tissues. In a few cases efforts have been made to excise the fibrotic tissue, since it was believed that bacteria could remain untouched by penicillin in such avascular areas. In most cases the scarring is so extensive that the surgical removal of all fibrous tissue is not feasible.

Penicillin is unquestionably the most effective agent that has yet been discovered for the treatment of chronic osteomyelitis. We believe that, when possible, treatment should be continued until the cultures from the local lesions have been sterile for 5 to 10 days. The treatment may have to be repeated if a relapse occurs.

#### TOXIC REACTIONS

None of the patients whose cases are presented here experienced any toxic reactions to penicillin, this is not surprising, since such untoward reactions are comparatively rare. This absence of significant toxicity for the patient is one of penicillin's most striking properties. The reactions to the drug that have been observed have not been serious. Occasional lots of penicillin cause *pain* on intramuscular injection. When penicillin is administered by a continuous intravenous drip, *thrombophlebitis* may be encountered in the veins that are used for this purpose. Infrequently the thrombophlebitis is accompanied by chills and fever, but these disappear promptly when a change is made to the intramuscular route of administration.

A few patients experience *diarrhea*, a reaction that is particularly apt to occur when large doses of penicillin are given. It is easily controlled by the administration of paregoric.

One reaction which has been observed is of interest. From 2 to 5 per cent of patients who are given penicillin develop *urticaria*. This reaction commonly occurs between the 7th and 14th day of treatment, but it may appear on the 1st day or not until several days after treatment has been completed. After persisting for 5 to 10 days it disappears spontaneously, and although it is occasionally quite severe, its only harmful effect is the discomfort that it causes. In several cases penicillin has been continued and the urticaria has cleared after a few

days. Its readministration at a later date may or may not be accompanied by urticaria. This condition does not seem to constitute a contraindication to the patient's again receiving the drug.

No toxic reactions involving the hematopoietic system, the kidneys or the liver have been observed following the use of penicillin. At present there are no known contraindications to its use.

### SUMMARY

In this clinic we have discussed the treatment of staphylococcic infections with penicillin. The following points may be repeated in summing up the discussion:

1. An understanding of the pharmacologic properties of penicillin is necessary if a maximal therapeutic effect is to be obtained.

2. The action of penicillin is bacteriostatic rather than bactericidal and the treatment with the drug must be continued until the infection has been eradicated.

3. Penicillin has reduced the mortality rate in staphylococcic bacteremia from 85 to 20 per cent.

4. In localized staphylococcic infections the use of penicillin results in recovery or improvement in more than 80 per cent of cases.

5. In treating staphylococcic bacteremia the objective in every case is to bring the infection under control as rapidly as possible. Large doses of penicillin may be necessary during the first few days of treatment.

6. When a significant accumulation of pus is present, surgical evacuation of the pus is necessary.

7. Penicillin will not effect recovery in moribund patients. It may also fail in other situations.

8. In acute localized staphylococcic infections the aim is the same as in the treatment of staphylococcic bacteremia—to bring the infection under control rapidly.

9. In chronic infections the duration of treatment is of first importance.

10. In treating chronic osteomyelitis, all sequestra must be removed.

11. Penicillin causes no serious toxic reactions. There are no known contraindications to its use.

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## THE USE OF THIOURACIL IN THE TREATMENT OF THYROTOXICOSIS

ROBERT H. WILLIAMS, M.D.\*

**Definition of Thyrotoxicosis**—Thyrotoxicosis is a disease of unknown etiology in which the pituitary gland stimulates the thyroid gland in such a manner that (1) the cells become hyperplastic and hypertrophic, (2) the gland enlarges, (3) the colloid stores of the thyroid become depleted, (4) the amount of thyroid hormone circulating in the blood stream increases, and (5) a hypermetabolic state develops. These changes affect the functions of all of the tissues in the body, producing a group of clinical manifestations, the outstanding of which are nervousness, palpitation, hyperorexia, weight loss, heat intolerance, excess sweating, exophthalmos, weakness and tremulousness.

### DIAGNOSIS

**History**—Thyrotoxicosis occurs in any age group and in either sex. It is, however, much commoner in females, developing particularly in individuals between 18 and 50 years of age. Most patients experience a distinct onset of their disease 3 to 12 months before consulting a physician. Commonly, the first abnormality observed is *nervousness*, although at times it is palpitation, exophthalmos, weight loss, diarrhea, or some other manifestation. Regardless of which symptom is noticed first many others appear soon, the relative intensity of these varying a great deal in different individuals. The nervousness is typically a restlessness, often described as "jitteriness," but it is also characterized by emotional instability, insomnia and sometimes by psychoneurotic manifestations. Almost always there is *heat intolerance* and *excessive sweating*. *Palpitation* and *exertional dyspnea* are commonly experienced and *mild swelling of the legs* is noticed by many patients.

Loss of weight amounting to 10 to 20 pounds or more occurs in almost all cases, in spite of the ingestion of large amounts of food. However, in some individuals there may be no weight loss, and indeed rarely an actual gain in weight is experienced. Anorexia exists in a very small proportion of cases, as do nausea and vomiting. Although diarrhea is not infrequently present, it is more common for the patient to state that there is an increased frequency in bowel movements but no watery stools. *Prominence of the eyes* and a *starve* generally exist.

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital and the Department of Medicine, Harvard Medical School, Boston, Massachusetts.

\*Associate in Medicine, Harvard Medical School; Assistant Physician, Thorndike Memorial Laboratory, Junior Visiting Physician, Boston City Hospital.



and a few patients may complain of marked prominence, lacrimation, puffiness of the eyelids, burning of the eyes, redness of the eyeballs, blurred vision and diplopia. The eye complaints may never develop or may appear many months before or after the other manifestations of the disease. A goiter is usually not observed by the patient until several months after the onset of the disease. Rarely there are symptoms due to pressure of the gland on neighboring structures such as dysphagia, respiratory distress, and disturbances in phonation.

**Physical Examination.**—Restlessness and anxiety are readily apparent. The *skin* tends to be smooth, soft, hot, moist, and somewhat loose. These changes can be conveniently demonstrated over the forearm. General hyperemia is almost always present and sometimes the palms, elbows, and face are quite red. Vitiligo, particularly over the dorsum of the hands, is occasionally present. The *eyes* occasionally appear normal, but the majority of patients exhibit some exophthalmos, widened palpebral fissures, slight limitation of extra-ocular movements, and a stare. A small proportion of patients may have features of malignant exophthalmopathy with palpebral edema, conjunctival injection, chemosis of the conjunctivae, marked exophthalmos (sometimes with one eye involved much more than the other one), pronounced increase in intra-orbital pressure, and marked limitation of extra-ocular motion, especially in the superior direction. In a small proportion of cases the tongue is red and its papillae atrophic. *Enlargement of the thyroid* is one of the most constant accompaniments\* of the disease, occurring in over 99 per cent of the cases. Rarely the amount of enlargement may be no greater than exists with the physiological hypertrophy of puberty, but in most cases a goiter is readily discerned. The entire gland is usually enlarged but the extent of involvement varies, particularly when one is dealing with a toxic nodular goiter. A bruit is usually present. The *pulse* is persistently rapid, forceful, and usually regular, fibrillation is not infrequently present. The systolic blood pressure is commonly increased, whereas the diastolic pressure tends to remain normal. The heart sounds are forceful.

\* It is extremely important to evaluate accurately clinically the changes in the thyroid. Too frequently a goiter is overlooked or, on the other hand, a pad of fat, a prominent cricoid cartilage or some other structure in the neck is mistaken for a goiter. In over 99 per cent of individuals the thyroid gland is in essentially the same relative position, the superior border of the isthmus being just beneath the cricoid cartilage, and the entire gland wraps itself snugly around the trachea. The subject is asked to take a sip of water and to tilt his head backward as much as is possible without appreciably tightening the muscles in the thyroid region. Having identified the structures and with the hands placed in the expected location of the thyroid gland, the patient is asked to swallow. With repeated acts of swallowing the contour and consistency of the gland are estimated. It is next important to determine whether a bruit is present, since this is of aid in differentiating a toxic from a nontoxic goiter. In a toxic gland a bruit can usually be heard over the entire gland. It should be differentiated from bruits produced by compression of the carotid vessels and from cardiac or respiratory sounds.

*Splenomegaly*, of slight degree, is present in about 15 per cent of the cases. A *tremor* of the fingers, tongue and eyelids may be demonstrated. Typically it tends to be fine and rhythmical. The reflexes are hyperactive. *Atrophy of the muscles*, sometimes marked, may be observed and *myasthenia* can be demonstrated in most of the cases.

**Laboratory Studies.**—The test of the *basal metabolic rate* is one of the most efficient tests for investigating the presence of thyrotoxicosis. The basal rate is increased in essentially every case. However, it is important to bear in mind that the normal rate for some individuals may be minus 18 per cent and when they develop thyrotoxicosis the basal metabolic rate may not rise to above plus 10 to 15 per cent, which in turn are normal values for other subjects. The basal metabolic rate may be recorded as unduly low because of infrequent renewal of soda lime. The rate may be recorded as unduly high if the patient has perforated ear drums, since oxygen may be lost in this manner. If the patient has eaten within 12 hours before the test, has exercised too much, has an infection, or has a great deal of anxiety associated with the test, the results may be too high. In individuals with cardiac dilatation and hypertrophy it is common to inject  $\frac{1}{4}$  grain of morphine subcutaneously, 30 minutes before beginning the test. Subjects who exhibit anxiety neurosis are given 3 grains of sodium amytal on the night preceding and again one hour before the test.

Estimation of the *protein-bound iodine* of the plasma is of great aid in some cases where diagnosis by other measures is quite difficult. However dependable methods for its determination are long and difficult making it a procedure which is unavailable to the majority of physicians.

The *blood cholesterol* is lowered in most of the cases of thyrotoxicosis and therefore its estimation is of some aid in establishing a diagnosis, but we rarely depend heavily upon this test.

### TREATMENT

Essentially all of the principal therapy in thyrotoxicosis has had as its aim to decrease the formation and the escape into the blood stream of the thyroid hormone. *Iodide* has been of distinct aid in these respects, but many patients have shown only a partial response and some have shown essentially no response. Furthermore there are many investigators who claim that with the prolonged administration of iodide the patient may become refractory—become 'iodine fast'. X-ray treatment combined with iodide therapy has been of some aid but has not been notably satisfactory. Iodide treatment used for 2 or more weeks preceding *subtotal thyroidectomy* has yielded very good results. It has left a great deal to be desired.

About 3 years ago it was reported<sup>1, 2, 3</sup> that sulfonamides and thiouracil exerted a *contraindic* effect in rats and also caused a lowering of the basal metabolic rate.<sup>4, 5</sup> Atwood<sup>6</sup> found that one of the deriva-

tives of thiourea, *thiouracil* (2-thio, 6 oxypyrimidine), was more goitrogenic than any one of a large number of chemicals which he tested. Using thiourea or thiouracil in the treatment of 3 cases of thyrotoxicosis he found<sup>7</sup> a remission of the disease and a return to normal of the basal metabolic rate. Williams and Bissell,<sup>8</sup> using thiouracil in the treatment of 9 cases of hyperthyroidism, some of which were severe, found not only a disappearance of the symptoms and signs of thyrotoxicity and a normal basal metabolism, but also a return to normal of the protein-bound iodine of the plasma, which presumably indicates a return to normal of the circulating thyroid hormone. Additional reports dealing with the pharmacological<sup>9, 10</sup> and clinical<sup>11, 12, 13, 14, 15, 16</sup> properties of this drug have now appeared.

**Pharmacological Properties of Thiouracil**—Thiouracil is dispensed in tablets of 0.1 or 0.2 gm each\* and is taken by mouth. Although it has a bitter taste, this is hardly noticed when it is rapidly swallowed. Although some of the drug is destroyed in the gastro-intestinal tract, most of it is absorbed very rapidly, the maximal concentration in the blood being attained in about 30 minutes. It is distributed throughout the body and is found in essentially all of the tissues and body fluids. The pituitary, thyroid, adrenal and bone marrow are prone to possess a greater concentration than do the other organs. Essentially all of the tissues have the power to destroy the drug. When daily total doses of 0.4 to 1.2 gm are given, approximately two thirds of the drug is destroyed, since only about one third appears in the urine and none in the stools. The concentration of thiouracil in the blood does not increase appreciably even in the presence of severe kidney, liver or heart disease. Within 15 minutes after ingestion of the drug, small amounts of it can be demonstrated in the urine of individuals with normal kidneys.

The foregoing facts suggest that in order to keep the concentration of thiouracil in the blood at an even level it is necessary to administer frequent doses at intervals scattered throughout the day. Estimations of the drug level in the blood and urine are not necessary in the routine treatment of patients.

**Clinical Use of the Thiouracil**—The ensuing discussion is based largely upon the experiences of the author, in collaboration with Dr. Howard Clute, in the treatment of 125 cases of thyrotoxicosis in patients from 5 to 72 years old. Many had previously been treated with iodine alone or combined with subtotal thyroidectomy. Most of the patients had diffuse hyperplastic glands but a few had adenomatous goiters. The duration of the disease at the time the patient was seen varied from 3 weeks to 22 years. *The majority of the subjects were not hospitalized during the course of treatment.* However, it is important that each

\* Thiouracil has not been placed on the market. A supply for investigation has been generously given to us by the Lederle Laboratories, Inc., Pearl River, New York.

patient be examined carefully before treatment is begun, since it is difficult to evaluate either beneficial or harmful effects of thiouracil if the physician is not familiar with the clinical condition preceding treatment. The examination should consist of at least a complete history, physical examination, urinalysis, white blood cell count and a differential blood count. Thus far, we have encountered no contra-indication to beginning thiouracil treatment in any case.

**DOSAGE.**—The daily dosage of thiouracil during the first 2 weeks is usually 0.6 gm., given in five doses, according to a schedule similar to the following: 0.1 gm. at 7 A.M., 11 A.M., 3 P.M., 7 P.M., and 0.2 gm. at bedtime. At the end of 2 weeks the dosage is reduced to 0.4 gm. daily, given in doses of 0.1 gm. at intervals of 5 hours. At the end of 4 weeks, the daily dosage is reduced to 0.3 gm., and after 6 weeks it is 0.2 gm. After 12 weeks it is reduced to 0.1 gm., provided the basal metabolic rate is approximately zero or below and that no clinical manifestations of thyrotoxicity are present. The daily dosage of 0.1 or 0.2 gm. may be maintained indefinitely in most cases without apparent harmful effects.

The dosages which we have listed should be considered maximal for essentially all cases. The fact that many patients have shown a satisfactory clinical response to doses somewhat less than the ones given above indicates that the above dosages are somewhat in excess of the amount really needed in some cases. In most instances this slight excess seems to make no appreciable difference, however, a special effort is made to use the minimal effective dose in subjects who have very large goiters and in ones displaying well-defined manifestations of malignant ophthalmopathy (*supra vide*). By suppressing the production of the thyroid hormone to a marked extent the pituitary gland is stimulated to produce an increased quantity of thyrotropic hormone which, in turn, stimulates the thyroid to greater hypertrophy and causes an exacerbation of the ocular manifestations. In an effort to counteract these effects we occasionally administer desiccated thyroid, 32 to 96 mg. daily, along with thiouracil.

**RESPONSE TO THIOURACIL TREATMENT WITHOUT SURGERY.**—The results may be arbitrarily divided into early and late the former consisting of the changes occurring within about the first 5 weeks and the latter consisting of subsequent changes.

**Early Results.**—Within 2 or 3 days after beginning treatment with thiouracil the symptoms of thyrotoxicity show a decrease in intensity and progressively subside until after about 5 weeks most of them have disappeared. Patients with ocular disturbances of a "nonmalignant" type exhibit an improvement in this respect corresponding to the disappearance of the thyrotoxicity. On the other hand subjects with the "malignant" ocular changes tend to experience an exacerbation in the ophthalmopathy as the thyrotoxic features improve with thiouracil treatment this phenomenon being similar to that of "postoperative

*progressive exophthalmos*" The size and consistency of the thyroid gland may either increase or decrease The *basal metabolic rate* and the protein-bound iodine of the plasma are generally normal within 5 weeks, but in cases wherein iodide therapy is replaced by thiouracil the time is somewhat longer The type of response which one can expect to observe in patients treated with thiouracil is illustrated in the following brief case presentation

W Q, a captain in the Army, aged 51 years, was seen October 25, 1943, for thiouracil treatment Until 6 months previously he had presumably been in excellent health, but within a few weeks thereafter he became quite nervous, developed a ravenous appetite and in 5 months lost 40 pounds in weight Palpitation and moderate dyspnea soon appeared He became less tolerant to heat and per-

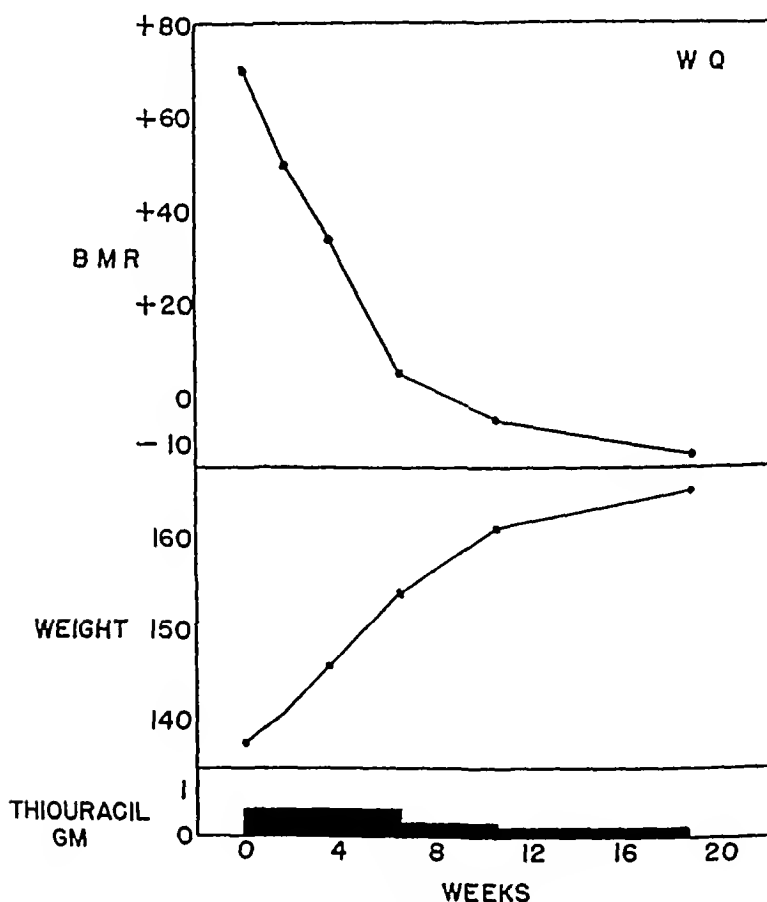


Fig 80 (W Q) —Lowering of the basal metabolic rate and gain in weight following the use of thiouracil in the treatment of thyrotoxicosis

spired excessively His friends commented that he had a slight stare to his eyes. One of the early symptoms was weakness, which during 6 months became profound and was associated with marked fatigability

On physical examination the skin was moist, pink, hot and somewhat loose There was pronounced muscle atrophy, particularly noticeable in the shoulders

and hands. Generalized weakness and myasthenia of moderate degree were readily demonstrated. The extended fingers and tongue were rather tremulous. A slight stare with mild limitation of the extra-ocular movements was observed. The thyroid gland was diffusely and symmetrically enlarged to two and a half times normal size. It was firm, smooth, and contained a bruit. The pulse was rapid (140) forceful and regular.

The patient weighed 138 pounds and his basal metabolic rate was plus 70 per cent.

The therapy instituted consisted of 0.2 gm. of thiouracil three times daily, 5 mg of thiamine and 50 mg of alpha tocopherol daily. The patient was permitted to continue with his routine work in an Army supply depot. After 3 weeks the vitamin therapy was discontinued. As seen in Figure 80 the basal metabolic rate declined rapidly and in almost a straight-line manner reaching a normal level within 6 weeks. The improvement in the clinical condition of the patient was in accord with the changes in basal metabolic rate. Within 6 weeks a pronounced transition had resulted. The patient boasted of a tremendous improvement in his general condition. His tremor had gone, his skin was normal, his pulse rate was 75, the stare and abnormal eye movements had vanished, a tremendous increase in strength was readily apparent, and he had gained 16 pounds in weight. The thyroid gland became very slightly smaller but it did not change appreciably in consistency.

After 6 weeks the dosage of thiouracil was reduced to 0.1 gm. three times daily and by the end of 5 months it was reduced to 0.1 gm. daily. During the interval of 5 months he regained all of his strength and 27 pounds in weight. Furthermore, his thyroid gland was less than one and a half times normal size and was of essentially normal consistency. It is planned to continue the thiouracil 0.1 gm. daily for at least a year.

*Late Results*—Once the clinical manifestations of thyrotoxicity have disappeared and the basal metabolic rate has become normal it is ordinarily easy to maintain the patient in good condition even with a total daily dosage of thiouracil of from 0.1 to 0.3 gm. per day. The thyroid gland generally tends to become progressively smaller until, after 6 to 12 months, it may be reduced in size by 30 to 70 per cent. In some instances glands which were once two to three times normal size have been found to be no longer enlarged. The use of excessive amounts of thiouracil retards the regression of the thyroid size and tends to accentuate the manifestations of malignant exophthalmos, while the administration of desiccated thyroid often improves these conditions. No patient has been found thus far to have become refractory to thiouracil although several individuals have been treated continuously with the drug for more than a year.

The following case was picked at random for presentation of the typical response observed in an individual treated with thiouracil for a long period.

about 5 weeks on this therapy there was no clinical improvement and the basal metabolic rate had remained essentially unchanged. He was disgusted with his iodide treatment and discontinued it. He refused treatment by operation in spite of a great deal of persuasion by two physicians. On physical examination his skin was found to be quite moist, hot and loose. There was a well-defined tremor of the hands and eyelids. The eyes were somewhat prominent, the palpebral fissures were widened and there was slight impairment of extra-ocular movements. The tongue was red and smooth. The thyroid gland was firm and three times normal size, the enlargement being symmetrical. The surface was slightly nodular. A bruit was readily heard over the entire gland. The pulse was forceful, regular, and its rate was 130. There was very slight cardiac enlargement.

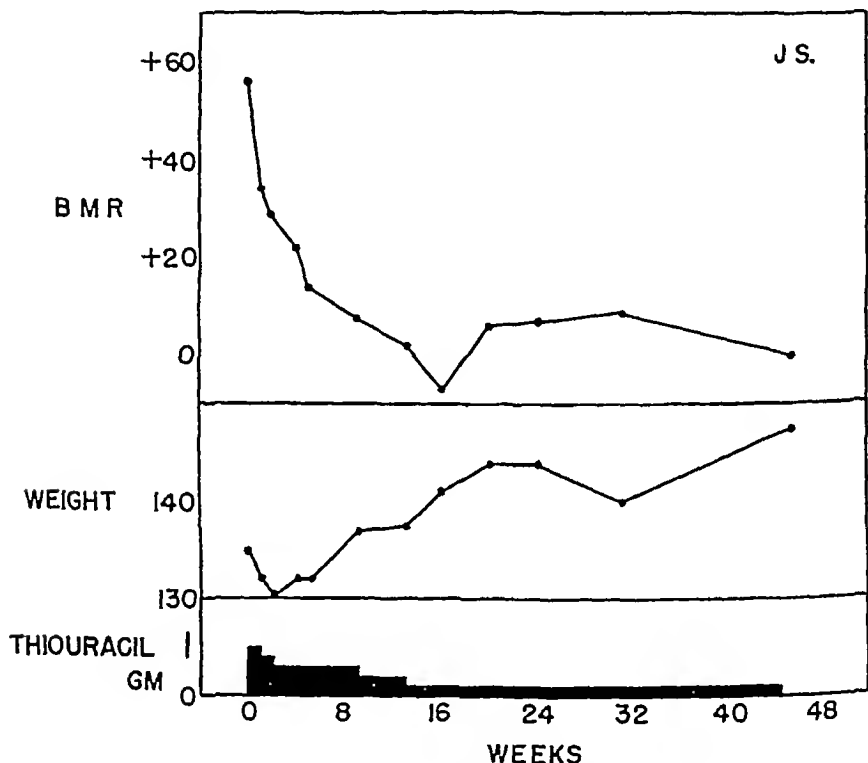


Fig 81 (J S) -Results following the use of thiouracil in the treatment of thyrotoxicosis

The basal metabolic rate on May 29 was plus 56

Treatment was started immediately with thiouracil, 1 gm daily, thiamine chloride, 5 mg daily, nicotinic acid, 50 mg daily, and brewers' yeast, 3 gm daily. The vitamin therapy was discontinued after 2 weeks, but the patient has continued taking thiouracil for approximately a year, the dosage was gradually reduced during the first 3 months to 0.2 gm daily and has been subsequently maintained at this level.

By the end of 2 months all of the symptoms and signs of thyrotoxicity had disappeared, the basal metabolic rate had become normal (Fig 81), and the thyroid had decreased slightly in size. During the subsequent 9 months that he has been followed he has remained free of toxic manifestations, has gained 12 pounds in weight and his thyroid gland has become 50 per cent smaller. During the entire interval of treatment he has not missed a day from his work.

**RESPONSES TO TREATMENT WITH THIOURACIL AND SUBTOTAL THYROIDECTOMY**—Since thiouracil may be depended upon to cause the disappearance of the thyrotoxic manifestations in essentially all cases of thyrotoxicosis, one may rightly ask why it should be necessary to perform a thyroidectomy. In answer to this query the following factors have been given chief consideration

(1) *Very large goiters* Even though one controls the toxic manifestations of the disease, it is often desirable to remove the thyroid gland if it is sufficiently enlarged to cause concern regarding the cosmetic effects or if it causes pressure on the surrounding structures

(2) *Toxic reactions to thiouracil* Although some toxic reactions to thiouracil are trivial and do not interfere with continued use of the drug, others, such as urticaria or agranulocytosis, may make treatment by thyroidectomy necessary

(3) *Factors interfering with proper cooperation by the patient* All patients receiving thiouracil treatment should be followed closely, since this is necessary in prescribing the optimum dosage and in recognizing complications early. Factors such as the patient living a long distance away, business obligations, ignorance of the patient, psychoneurosis or the general attitude of the individual may make surgical treatment desirable. It often becomes readily obvious that the temperament of some patients is such as to make them become impatient with prolonged treatment. Furthermore, some subjects state at the outset that they prefer surgical treatment. Since the latter form of treatment is well established and since it is not known what the results of treatment with thiouracil extended over a period of several years will be the patient's request is often granted. However, in this connection it is significant to state that most of the patients desire to take "medical" treatment in spite of the fact that they are told that a serious complication from thiouracil treatment might result and in spite of the fact that surgical treatment may ultimately be necessary



**COMPLICATIONS FROM THIOURACIL TREATMENT**—Most of the complications appear during the first 5 weeks of treatment. With the dosages which we have previously given in detail we have observed fewer complications than were noted when the dosages used were more than twice the size of the present ones. Although a great variety of complications have been observed, the only ones that have caused much concern have been agranulocytosis and urticaria. The former has occurred in 2 of our 125 cases and the latter in 3. All of these subjects subsequently responded satisfactorily with discontinuation of thiouracil therapy and its replacement with treatment with potassium iodide alone or with thyroidectomy. The other complications encountered have consisted of morbilliform rash, edema of legs, enlargement of the submaxillary salivary glands, fever, nausea, vomiting, diarrhea, headache and arthralgia. However, all of these symptoms disappeared in a very few days with a reduction in the dosage of the drug or with its omission for a couple of days.

To aid in the early recognition and proper treatment of the foregoing complications, the physician should see the patient at 1 or 2 week intervals during the first 6 weeks and the patient should be encouraged to call the physician if any infection appears, if any of the above complications are recognized, or if he notices the appearance of any disturbances. These factors are to be emphasized since the prodromal manifestations of agranulocytosis may be absent. Leukopenia may appear during the course of treatment and the white count may return to normal in spite of continued treatment with thiouracil. However, if the white count decreases below 3500 it is safer to replace the thiouracil therapy with iodide. This policy should be followed in the case of other changes which represent potential trouble, because the treatment of most cases is satisfactory in the absence of thiouracil.

### CONCLUSION

In conclusion, it may be stated that on the basis of present data it appears that in thiouracil we have a drug which is highly dependable in causing a remission of thyrotoxicosis. It gives promise of supplanting surgical treatment in a large proportion of cases and of being of great aid in the preoperative preparation of the others, provided that toxic reactions to the drug are not too common.

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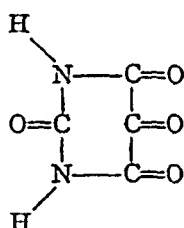
# THE MANAGEMENT OF DIABETES MELLITUS IN GENERAL PRACTICE

ELLIOTT P JOSLIN, M D , S c D , F A C P \*

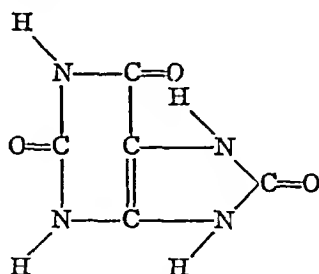
Two outstanding diabetic discoveries were made in 1943 first, the production of diabetes by the administration of alloxan and, second, the demonstration of a hitherto unsuspected incidence of diabetes in young men In addition to these achievements, I also point out to my patients the growing importance of the complications of diabetes because of their increasing exposure to them due to the steadily lengthening diabetic life No matter whether my patients are young or old, I like them to be *au courant* with investigations going on in connection with their disease which, after all, is largely up to them to manage and control

## ALLOXAN AND HOPE FOR BETTER DAYS FOR DIABETICS

Alloxan is the ureide of oxalic acid and has the formula



One might look upon uric acid as a three-story house with an "L" Take away the "L" and alloxan remains



Alloxan has been known for years and was recognized as a component of the body in 1862 by Liebig,<sup>1</sup> but no satisfactory test for it has been described and its unstable composition makes it elusive It has been utilized as an oxidizing and reducing agent

From the George F Baker Clinic, New England Deaconess Hospital

\* Clinical Professor of Medicine Emeritus, Harvard Medical School, Medical Director, George F Baker Clinic, New England Deaconess Hospital, Consulting Physician, Boston City Hospital

In 1937 Jacobs<sup>2</sup> found that following the injection of alloxan into an animal, hypoglycemia occurred, but it was reserved for Dunn Sheehan and McLetchie<sup>3</sup> in Glasgow in April, 1943, to note its selective action in causing the necrosis of the islands of Langerhans of the pancreas of a rabbit. Such animals died within 14 to 22 hours after the injection of 0.2 mg. of alloxan per kilogram of body weight. For a brief period the blood showed hyperglycemia but this was soon followed by hypoglycemia and death. Cabell Bailey and Orville Bailey<sup>4</sup> believing diabetes would be inevitable in such an animal if life could be prolonged, administered repeated injections of glucose to such rabbits and found that diabetes appeared in the next 24 hours. A summary of seventeen articles upon alloxan occurs in the *New England Journal of Medicine* for April 1944<sup>5</sup> and another article reporting original work by Bailey, Bailey and Leech appeared in the same journal May 4, 1944. They observed that all alloxan diabetic rabbits developed cataracts within two months of the production of the diabetes.

The significance of alloxan diabetes is far-reaching. It strikes nearer the core of the diabetic problem than anything hitherto reported. Here is a chemical which undoubtedly is to be found in the body, of which an excess can destroy the insulin-producing cells. What is its source? What influences its formation or destruction? What will neutralize its action? Does it first stimulate the island cells to secrete and thus exhaust them, or more likely is its power of producing necrosis exercised from the start? How can one recognize its presence? These are only a few of the questions which arise. Obviously alloxan presents opportunities for research in diabetes hitherto undreamed of and gives hope to patients and practitioners alike for further advances in the management of the disease. The production of diabetes in rabbits, rats and other animals in such a pure form is now so simple that studies of the disease and its complications are open to all who desire to make them.

there any reason to doubt appreciable differences at other ages of life and "that current estimates of the amount of diabetes in the population are falsely optimistic"?

The significance of these data in the general management of the disease is many fold. First of all, it will make our people far more diabetic-conscious and far more eager to come to the doctor to learn if they have the disease. Already they have become alert to the influence of heredity. Once their disease is diagnosed, they desire prompt treatment and this affords the physician a chance to treat a case with recent onset, and such patients offer far better prognoses.

**2. Patients with an Original Diagnosis of Diabetes Eventually Accepted into Armed Forces**—During this year's follow-up of our 1626 childhood diabetics known to be alive at some time during 1942 or 1943, it was found that 7 were in the armed forces. As the sex of diabetics differs little in this age group, it follows that nearly 1 per cent of our boys were not considered or recognized to have diabetes when they became men and were examined for the Army. What is the explanation? Salient facts are recorded in Table 1.

A study of the protocols of the cases cited in Table 1 shows that the ages of the boys when the original diagnosis of diabetes was made varied between 6 and 14 years, and the interval between diagnosis and their induction into the Army, although not known exactly, was probably between 11 and 5 years. Heredity was known in three of the seven cases. Weights or heights were not extraordinary, although one boy weighed 192 pounds dressed, and his height with shoes was 5 feet,  $8\frac{3}{4}$  inches.

The first case, 10464, I will throw out at once, because although the patient showed 0.9 and 1.1 per cent glycosuria, and blood sugars of 210 and 200 mg. with venous blood, I find by my records he had furunculosis. That is a warning against making a diagnosis in the presence of an infection of any character until it has been verified by subsequent tests when the infection has disappeared.

It is true that all of these patients were recognized at the time to be rather borderline diabetics, because in no instance did a patient receive insulin save temporarily, and the carbohydrate in the diet of no patient was lowered below 200 gm. save in case of the 6-year-old child, and even his diet was gradually raised within 2 years to practically everything.

For the sake of argument, it is assumed that none of these patients has diabetes now, but of course that cannot be verified.

All of the cases showed glycosuria and in three of them it reached between 1.1 and 2.2 per cent, but glycosuria alone, even of considerable proportions, does not justify a diagnosis of diabetes.

All of the fasting blood sugars were normal, but this is a common occurrence in frank diabetes in young people, particularly in the first months of their disease. On the other hand, in no instance did the

TABLE 1—SEVEN CASES ORIGINALLY DIAGNOSED DIABETICS EVENTUALLY ACCEPTED INTO ARMED FORCES

Case No	Age at Diagnosis	Body Weight (Lbs.)	Date	Time	Sugar	
					Urine (Per Cent)	Blood (Mg)
10464	6	41 (D)	4/ 5/31	1 hr after lunch 8.30 p.m.	0 9	210
			4/ 6/31		1 1	200 V B
11975	8	70 (D)	6/28/33	1 hr after 42 gm. sucrose	tr	250
				1 hr "	tr	160 ?C.B
				2 hrs. " "	0	140
			11/29/34	Fasting	0	100
				1/2 hr after 50 gm. glucose	0	170 C B
				1 hr "	0	150
13219	14	182 (N)	2/23/35	2 hrs.	0	120
				Fasting	0	100
				1/2 hr after 100 gm. glucose	0 2	160 V B
				1 hr "	0 3	150
			2/ 8/36	2 hrs. "	1 2	140
				Fasting	0	110
				1/2 hr after 100 gm. glucose	0 2	200 V B
				1 hr "	1 9	150
				2 hrs. "	0 7	130
			12/29/36	Fasting	0	100
				1/2 hr after 100 gm. glucose	0 2	170 V B
				1 hr "	0 8	170
				2 hrs.	0 8	130
13386	9	50 (D)	1/23/35	Fasting	0	90
				1/2 hr after 50 gm. glucose	0 2	200 C B
				1 hr "	0	140
				2 hrs.	0	100
			1/31/35	Fasting	0	80
				1 hr after glucose	0 1	180 C B
13387	13	86 (D)	1/30/35	Fasting	0	90
				1 hr after 40 gm. glucose	0	140 C.B
				1 hr after 2n 1 50 gm. glucose	0	210
14673	13	94 (D)	6/29/36	Fasting	0	80
				1/2 hr after 100 gm glucose	0	140 V B
				1 hr "	2 2	140
				2 hr "	0 3	130
14681	13	112 (N)	10/ 7/37	Fasting	0	80 V B
				1 hr after 50 gm. glucose	0	160 C.B.
				1 hr "	0	150
				2 hrs. "	0	140
			1/30/38	Fasting	0	80
				1/2 hr after 100 gm. glucose	0	140
				1 hr "	0	150
				2 hrs. "	0	140

Urine tested by Fehling's solution. Blood by Benedict's solution.

blood sugar return to or below the normal value at the end of two hours. Therefore, according to this criterion diabetes was correctly diagnosed, but we have not been accustomed to consider such a procedure as a trustworthy diagnostic method.

Capillary blood sugar determinations were certainly employed in two and possibly three cases. In one of them, Case 11975, in which the patient was a child of 8 years, 42 gm of sucrose was given and thereupon the value reached 250 mg. Our rule is to consider the normal fasting value of capillary blood to be the same as venous blood, but the upper normal diagnostic value with capillary blood in a sugar tolerance test to be under 200 mg. This case, therefore, was diagnosed diabetes. However, we had our doubts because of a second test, this time with 50 gm of glucose, in which the capillary blood failed to rise above 170 mg and therefore did not reach a diabetic level. On the other hand, with Case 16042 the tests were carried out with both capillary and venous blood, and with 70 gm of glucose with capillary blood the diagnosis failed to show diabetes, but with 100 gm of glucose with venous blood, the blood sugar rose to 220 mg.

All in all, therefore, the fact that 7 patients originally diagnosed diabetics but possibly wrongly so diagnosed, were admitted into the Army, shows the necessity of caution, especially if any doubt exists, in designating an individual a diabetic when the fasting blood sugar is normal, even if the 2-hour blood sugar test shows no return to the original fasting value or the intervening tests rise with capillary blood to 200 or even above 200 mg, or with venous blood to 180 or as much as 220 mg. Moreover, no diagnosis of diabetes should be made if an infection is present unless the glycosuria and blood sugar values are outstanding at the time or tests are repeated when the individual is free from infection. As a matter of fact, invariably it has been our rule for some years to record the temperatures at the beginning and end of the test. Nevertheless, in 99 per cent of our cases, so far as we are aware, the original diagnosis has proved correct, and this is reassuring.

**3 Diabetes Diagnosed Early Responds Well to Treatment**—Years ago I was able to show that the individual supposedly well but found to be diabetic by an examination for insurance outlived his neighbor whose diabetic symptoms forced him to consult his physician. Recently a group of Army cases has been referred to me for treatment, in which the presence of diabetes was learned because of Selective Service examinations. Improvement in these cases has been rapid despite apparent severity.

The diabetes in the patient I now present to you, Case 24001, 29 years of age in December, 1943, did show symptoms for a very few weeks before it was discovered and so it is not absolutely typical of the diabetes recognized by insurance or Selective Service. The case serves my purpose, however, in that the patient shows a rapid im-

provement, although at his first visit on December 28, 1943, the glycosuria was 8 per cent, diacetic acid ++ and the blood sugar 333 mg. No hospital bed being available, he was treated through the office and kept on with his work. His course is shown in Table 2.

*Diet*—Simplification of diet is necessary today for doctors and patients. I am accustomed to follow this plan. By prescribing four portions of 5 and 10 per cent carbohydrate vegetables daily, one can assume with considerable probability of accuracy that the carbohydrate content of the same will be 20 gm. To this can be added 10 gm of carbohydrate which is represented by a half-pint mixture of equal parts of milk and cream. A bowl (large portion) of cooked oatmeal contains another 20 gm of carbohydrate, making a total for the vegetables, milk and cream mixture and oatmeal of 50 gm. A second

TABLE 2—OFFICE MANAGEMENT OF DIABETES OF RECENT ONSET

Date	Sugar		Diet (C.)	Weight Dressed (lbs.)	Insulin
	Urine (Per Cent)	Blood (Mg.)			
Dec. 28 1943	8.0	333	200	166	8 + 12
29	8.4				12 + 12
30	2.9			165	12 + 12
31		74		165	
Jan. 3, 1944	0	76	"	169	12 + 12
17	0	71		167	8 + 12
21	0	152		169	4 + 12
28	0	89		166	12
Feb. 9	0	110		165	12
Apr. 10	0	62			12

\* All of the blood sugars were taken in the late forenoon, except those of January 21 and February 9 which were taken after lunch.

50 gm. will be represented by three medium sized oranges, thus raising the total carbohydrate to approximately 100 gm. To this can be prescribed bread, estimating that one slice, approximately an ounce (30 gm.) contains not far from 15 to 18 gm. of carbohydrate. This man was given six slices or a total of 100 gm. (90-108) which, added to his previous allowance made the final carbohydrate in the neighborhood of 200 gm. With most patients the bread at the beginning is limited to three slices a day, making the total carbohydrate 150 gm. Subsequently, the diet can be altered with substitution for fruit cereal and bread. If glycosuria is avoided, it is easy to add weight by increasing the percentage of cream, or to reduce weight by its omission.

The patient was told to take meat, fish, eggs, cheese and butter in moderate quantity with the hope that the protein would be not far from 100 gm. and the fat 100 gm.



It is surprising how many patients do so well on this schedule that their hospital reservation for three weeks later is cancelled. I still think the hospital-educated diabetic is overwhelmingly safer than the office-treated case, but with no beds available one is forced to treat his patients in an ambulatory fashion, although even then I try to get them to attend at least some of the hospital classes.

*Insulin*—This patient received at the office 8 units of crystalline insulin and 12 of protamine zinc insulin, and the following morning 12 units of crystalline and 24 units of protamine zinc insulin. This was continued for five days, when a glycosuria and a blood sugar of 76 mg led to a revision of the order to 8 units of crystalline and 18 of protamine zinc insulin, which were continued for 2 weeks when again the crystalline was lowered to 4 units and the protamine zinc to 16 units. I always like to give insulin in multiples of 4, because it is so much more easily registered on the syringes we prefer our patients to use, namely, a 1-cc syringe divided into tenths. Still later, crystalline insulin was omitted and protamine zinc insulin reduced to 12 units.

For still milder cases in older patients, 8 units of protamine zinc insulin may be prescribed at the first visit and subsequently raised or lowered, remembering that with diet alone glycosuria will fall and with insulin will decrease still more rapidly. Furthermore, one must bear in mind that the full effect of the protamine zinc insulin will not be manifested until the third day.

In general, one attempts to control the diabetes with diet and protamine zinc insulin and only adds crystalline insulin when the protamine zinc insulin has risen to 20, 24 or 28 units, above which one hesitates to go for fear of an insulin reaction during the night. However, many patients learn to control their diabetes with even larger quantities of protamine zinc insulin alone and no universal rule can be made.

It is our practice to inject the crystalline and protamine zinc insulin separately. In certain clinics the two are mixed in the same syringe, but our experience, particularly with children, has prejudiced us against such a procedure. In diabetes one is dealing with many variables—exercise, diet and insulin—and if one introduces still another variable factor by mixing the two insulins, in our hands the results have not been favorable. For the same reason we hesitate to adopt other insulins which in themselves would be infinitely better than no insulin, because we do not wish to expose our patients to reactions at unaccustomed hours of the day. In general, with Hamlet, we prefer to “bear those ills we have than fly to others that we know not of.”

With patients taking protamine zinc insulin alone, if the urine voided on rising, or a specimen voided half an hour later to guard against the presence of sugar which may have accumulated in the bladder overnight, is not sugar-free, we are accustomed to add 4 units of protamine zinc insulin until the urine voided on rising is sugar-free.

or until about 20 to 28 units are injected. If then it appears that glycosuria is present fasting or even after meals, crystalline insulin is added in 4-unit doses and usually eventually will reach one-third to one-half that of the protamine zinc insulin.

#### CAUSES OF DEATH DURING 1942 AND 1943 AMONG DIABETICS WITH ONSET OF THE DISEASE IN CHILDHOOD

Diabetic children live and some of them live a long while, so long in fact and so comfortably that often the tendency is to pursue with them a *laissez faire* policy as regards control of the disease. Subsequent to the first observation of a 10-year-old diabetic child in our group, the Metropolitan Life Insurance Company calculated its life expectancy, regardless of the duration of diabetes, and found it to be 40 years. But diabetic children do not all live those 40 years and, therefore, the causes of death of 23 during 1942 and 1943 among our 1626 diabetics with the onset of their disease in childhood deserve notice. At present 45 of the 1626 are untraced and there may be a death among this number. The reported causes of death are shown in Table

TABLE 3—TWENTY-THREE DEATHS IN 1942 AND 1943 AMONG 1626 DIABETICS WITH ONSET IN CHILDHOOD

Infections			
Staphylococcus aureus	1	Burns	1
Cavernous sinus thrombosis	1	Coronary thrombosis	2
Pneumonia	1	Diabetes	3
Meningitis	1	Appendicitis	2
Whooping cough	1	Coma	4
		Nephritis	4

3 The average duration of the diabetes was 10.7 years and average age of the patients at death was 20.2 years.

1 An Infection Neglected—I will not discuss here deaths from infections, one each with Staphylococcus aureus infection, cavernous sinus thrombosis, whooping cough, meningitis and pneumonia, but instead wish to show you Case 16593, a longshoreman who is leaving the hospital today because he illustrates the harmfulness of a *laissez faire* policy in dealing with infections, even though mild at the outset.

L S McKittrick and Dr Francis D Moore, disclosed it with a hypodermic needle. Fortunately it had not reached the shoulder joint and with wide opening of the area the condition rapidly healed. The patient leaves today sugar-free and in good condition.

Whether recurrence of such infections can be prevented with a small daily dose of sulfadiazine, as has seemed to be the case in certain other cases, time alone can tell. At any rate, this man and all of us who watched him know that infections in diabetes must not be tolerated.

The deaths from coronary thrombosis and the five in which the diagnosis was simply designated "Diabetes" on the death certificate, as well as the one from burns, I will pass by. But I wish to say a word about appendicitis in diabetes and also about diabetic coma, reserving to the last the most depressing of all complications in diabetes, illustrated by the four deaths from chronic nephritis, because it is so often associated with blindness.

**2. Appendicitis**—The premonitory symptoms of diabetic coma frequently simulate those of appendicitis and the leukocytosis common to each state further complicates the picture. Usually with the surgeon's aid a correct diagnosis can be made within a very few hours, but if there is reasonable doubt, an operation is indicated even if there is coexistent slight acidosis. The reactions with protamine zinc insulin sometimes also are confusing. For these reasons the prophylactic removal of an appendix must also be considered and within the last 12 months this has been carried out in the case of two of our patients. This was done for family reasons and because of remoteness from medical care. The two deaths from appendicitis cited in the table occurred in patients living at a distance.

**3. Diabetic Coma**—Coma is a complication of diabetes which is seldom justifiable. The one case recently in which allowance could be made for its occurrence was in a young man who had done well for years but developed an acute infection while living alone, went into coma in his boarding house overnight and, although unconscious, fortunately was found, brought to the hospital and recovered.

His case was one of 122 cases of diabetic coma which have been treated on our service at the New England Deaconess Hospital since August, 1940. Two deaths occurred in this group. In one fatal case the patient lived  $6\frac{1}{2}$  hours, acidosis was overcome, but she succumbed to multiple abscesses in the sinuses accompanied by osteomyelitis. The other patient, 71 years of age, died  $1\frac{1}{2}$  hours after admission with evidence at autopsy of two recent occlusions of her coronary arteries. All of these cases have been treated with insulin, dehydration was overcome with salt solution, almost invariably the stomach was emptied by lavage to prevent acute dilatation, and the best available nursing care was provided. The patients have not received alkalis or glucose, in fact, whenever we hear of a death from diabetic coma we now look to see if glucose or alkali was administered.

In one of our most recent cases, I confess, the patient did show hypoglycemia following the first day of coma.

The onset of this patient's diabetes was at 10 years of age in November 1941. She recovered from coma under our care in November 1943 and again entered the hospital in coma April 7, 1944, with blood sugar of 600 mg., carbon dioxide 10 volumes per cent and with a history of nausea, vomiting, drowsiness and Kussmaul respiration. She received 450 units of crystalline insulin between 9:00 A.M. and 3:00 P.M. and the next morning seemed so well and so comfortable that she was given a soft diet of carbohydrate 150, protein 60 and fat 60 gm. but along with it, most unfortunately and unadvisedly, was allowed to take her usual morning dosage of 24 units of crystalline and 48 units of protamine zinc insulin. When I chanced to see her at 10:30 A.M., she responded with difficulty and 400 cc. of 10 per cent intravenous glucose and 2000 cc. of 5 per cent glucose had to be administered before she was comfortable by 3:30 in the afternoon. Improvement was rapid. She left the hospital on April 12, taking her diet of carbohydrate 180, protein 90 and fat 90 gm., and 22 units of crystalline insulin plus 42 of protamine zinc insulin, having excreted 15 gm. of sugar in the urine during the preceding 24 hours.

Of course the hypoglycemia in this case was totally avoidable and inexcusable because (1) the blood sugar was 99 mg. at 5:00 P.M. the preceding afternoon, (2) it is well known that large doses even of a quick acting insulin exert a prolonged action, (3) the fasting blood sugar of the child, unfortunately unreported, was 48 mg. when the child was given her usual dosage of 24 crystalline plus 48 units protamine zinc insulin. I mention this case, first, because I like to record errors under conditions where such should not exist (just as it always does me good personally to give a patient three dollars when I miss a vein) since this helps to prevent others, but also because it indicates how easily with prompt treatment occurrences of this type if recognized can be relieved.

We believe in treating diabetic coma with insulin, because patients who have sufficient insulin do not develop it. We treat a deficiency of blood sugar, resulting from an excess of insulin, with glucose because glucose neutralizes insulin. We never neutralize our insulin with glucose before we give it to a diabetic coma patient, because a diabetic coma patient needs insulin.

4. **Chronic Nephritis.**—Four deaths from nephritis in 1942-1943 occurred among our 1626 diabetics with onset in childhood; another patient died in February, 1944 and now I present to you four living patients coming to us in the last two weeks with the same complication. All are blind or likely to become so in the near future. I do not wish to discuss at this time the special type of nephritis, preferring only to call to your attention the threatening magnitude of this complication occurring in young diabetics who, with hardly an exception, have disregarded diet and calories and lived by the grace of insulin. So far as possible I have used their own words or those of their parents in pointing the lack of diabetic control.

CASE 2726—This boy, who developed diabetes in July, 1921, at the age of 13 years, consulted me first in 1922 and was not again seen until 1937. His diabetes was seldom controlled and he is reported to have had repeated attacks of diabetic coma and insulin reactions at his home. All his teeth were removed in 1931 and in 1937 evidences of nephritis appeared. In 1937 he wrote, "for several years past I have followed no set diet." In 1939 the urine contained 300 mg of albumin with occasional granular casts, but the blood pressure did not rise to 160 until

TABLE 4—FOUR DEATHS FROM NEPHRITIS DURING 1942-1943 AMONG 1626 DIABETICS WITH ONSET IN CHILDHOOD

Case No	Sex	Age at Onset	Date of Onset	Date of Death	Duration
5000	F	11 3	Dec, 1925	June, 1942	16 5
5431	M	5 3	Dec, 1921	Nov, 1943	21 9
9111	F	13 7	Feb, 1930	Jan, 1943	12 9
12588	M	4 7	Jan, 1926	June, 1943	17 4

1938. The following year the albumin was 200 mg, and in 1941 the arteriosclerosis showed in the pelvic vessels by x-ray. In 1942 the albumin was 600 mg and many coarse and fine granular casts were present. The nonprotein nitrogen was 43 mg. The right eye showed waxy exudate and punctate hemorrhages, the left was seen with difficulty. At the present time here in the hospital the albumin is 500 mg, many granular casts are in evidence, and the nonprotein nitrogen is 48 mg. Vision is lost in the left eye and hemorrhages are present in the right eye, through which occasionally he can read print.

CASE 4746—This boy developed diabetes suddenly at 12 years of age in 1925. This was quite well controlled. In 1931 examination of the eyes by Dr. J. Herbert Waite showed them to be normal, and in 1932 there was no sclerosis of the anterior tibial arteries by x-ray. He had local abscesses in 1931 and 1932, and a perirectal abscess in 1935. In 1936, kidneys and blood pressure were still normal. Control of the diabetes was then somewhat, but by no means completely, relaxed. In 1941 old hemorrhages were found in each retina and in 1943 vitreous hemorrhages and retinitis proliferans developed. His blood pressure was 190/106, albumin 780 mg, and casts were present. In May, 1943, the right eye was enucleated on account of acute hemorrhagic glaucoma and in March, 1944, glaucoma was present in the left eye, the blood pressure was 200/100 and albumin 920 mg. As you see him today, his blood pressure is 240/126. The present pain in the eye, accompanied by nausea and vomiting, makes parenteral feeding obligatory.

CASE 7730—This boy developed diabetes at the age of 13 3 years in 1927 and was nearly in coma. He was seen at the office many times between 1930 and 1944, during which period at the office or at the hospital the urine was sugar-free on but two days. In 1931 I received the following note from his mother, "—can't keep him on his diet and he is dreadfully underweight, wants to sleep all the time and cranky. I am almost crazy trying to do for him." In 1937, in reply to a questionnaire, he wrote, "I am not on any diet." He had had an appendectomy in 1935.

In January, 1944, the patient returned with severe headaches and dyspnea, showing 0.3 per cent sugar and albumin varying between 700 and 75 mg, hyaline, fine granular casts, and a nonprotein nitrogen of 63 mg. He was under observa-

tion off and on in January, February and March, 1944, and was here last on April 27 with marked edema which had not responded satisfactorily to previous rest in bed, digitalis, acacia and potassium nitrate. On that day the urine showed 0.6 per cent sugar, albumin 300 mg and hyaline casts, the blood sugar was 196 mg., nonprotein nitrogen 61 mg and total protein 4.1 per cent, and the blood pressure was 140/90. At that visit he stated, "I have never kept my diet for seventeen years and now I am sticking to it and it does not do any good." The following night his heart became still more incompetent and he was readmitted to a hospital *in extremis*. The eyes showed a few small, deep hemorrhages.

CASE 24405—This girl developed diabetes at the age of 6 years in 1925 and came to the office on April 21, 1944, with the statement from her physician that "while she was without question the most neglectful and uncooperative patient, she thrived. She never had less than 4 plus urines, but was able to live a very busy life as a secretary, never developed acidosis, kept her weight up to normal and about a year ago gave no x ray evidence of peripheral arteriosclerosis. Approximately six months ago she developed an abscess in her jaw from an infected tooth and this was followed by a severe nephritis. She had 4 plus albumin in the urine, many granular casts, a blood nonprotein nitrogen of 63 mg., a blood pressure of 200/140, and extensive hemorrhages in the retina with edema in the optic nerve. When first seen here, the urine contained 0.9 per cent sugar 100 mg of albumin and compound granular casts, the blood sugar was 315 mg., nonprotein nitrogen 84 mg and hemoglobin 65 per cent, and the red blood count was 3,190,000. Her vision was reduced almost to complete blindness, the heart was enlarged, and moderate hydrothorax was present.

If these four cases of nephritis in young diabetes do not stimulate you and me to renewed effort to control the disease in season and out of season, I do not know what can. It is trite to tell our patients they can fool the doctor, but they cannot fool the disease, and recently I have quoted the following words of William James "We are spinning our own fates, good or evil, and never to be undone. Every smallest stroke of virtue or of vice leaves its never so little scar. The drunken Rip Van Winkle, in Jefferson's play, excuses himself for every fresh dereliction by saying, 'I won't count this time!' Well! he may not count it, and a kind Heaven may not count it, but it is being counted none the less. Down among his nerve cells and fibres the molecules are counting it, registering and storing it up to be used against him when the next temptation comes. Nothing we ever do is, in strict scientific literalness, wiped out."

In my experience, nephritis is rare in diabetes who diligently try to control their disease with diet and insulin but even so I hardly dare

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## PRESENT DAY SPECIFIC TREATMENT OF THE PNEUMONIAS

BERNARDO A. SAMPER, M.D.\* AND MAXWELL FINLAND, M.D., F.A.C.P.†

ADVANCES in the specific treatment of pneumonia have been taking place at an ever accelerating pace during the past decade. With each new advance, the range of effectiveness, that is, the variety and severity of cases yielding favorably to treatment, is broadened while the untoward effects caused by the newer therapeutic agents are successively less frequent and less serious. With the proper selection and intelligent use of the therapy now available, all but a small proportion of cases should respond favorably and the mortality from pneumonia can be kept at a very low minimum.

**Importance of Early Etiological Diagnosis.**—The curative agents now available in the treatment of the pneumonias include the sulfonamide drugs, penicillin and specific antiserums. It is important that physicians acquaint themselves with the indications for the use of each of these forms of treatment and know how to use them effectively. It must be emphasized from the start that all of these agents are effective only in the pneumonias caused by bacterial agents and not against pneumonias of known virus etiology or in the cases of primary atypical pneumonias of unknown etiology which are loosely called "virus" pneumonias, except insofar as these virus pneumonias are complicated by bacterial infection. Furthermore, different bacterial agents vary in their susceptibility to these therapeutic agents. Some like the Friedländer's bacillus or the influenza bacillus, respond poorly or not at all to any of these specific remedies, while among others different strains may vary in their susceptibility. The choice of therapy and its proper use therefore, depends on the bacterial agent which is to be attacked.

A knowledge of the causative organism, that is, an etiological diagnosis, is, therefore, most desirable for the proper management of pneumonia. For that purpose, culture of the blood and bacteriological examination of the sputum or of any purulent exudate constitute an essential part of this management. The materials for culture moreover must be obtained early and *before treatment is begun* in order to give the greatest amount of useful information. After treatment has been started it may be difficult and sometimes impossible to identify the causative agents from some of these sources.

An erroneous diagnosis of "virus pneumonia" is frequent because of the failure to heed this principle, and treat

\*Research Fellow, Thimble Memorial Lectures and Harvard Medical School, Boston, Mass.

†Associate Professor of Medicine, Harvard Medical School, and Senior and Associate Lecturer in Thimble Memorial Lectures, Boston, Mass.



sometimes suspended when the response is not favorable because the diagnosis is incorrectly made. Such cases all too frequently turn out to be due to relatively resistant strains of bacteria, or to susceptible strains in cases in which treatment has been inadequate. A knowledge of the causative organism, if it had been obtained earlier, often would have indicated that more prolonged and intensive treatment was called for or that a change from one form of specific treatment to another was necessary.

### SULFONAMIDES

In general, the sulfonamide drugs are still the first choice for the treatment of the bacterial pneumonias. They are highly effective against pneumococci of all types, and these organisms are the cause of the majority of the cases of primary lobar pneumonia. They are equally effective against the human virulent Group A streptococci of all types. The streptococci ordinarily are infrequent causes of primary pneumonia but they are important as incitants of secondary pneumonias in cases with other foci of streptococcal infection and after measles, influenza or other respiratory infections including the so-called "virus" pneumonias. They are less effective against staphylococci, although intensive and prolonged sulfonamide therapy has yielded favorable results in many severe cases caused by this organism. Staphylococcal pneumonias have been observed with increasing frequency in recent years, particularly as a complication of influenza or other virus infections and as an apparently primary infection in infants and young children. Friedlander's bacillus pneumonias, fortunately, are quite infrequent. Their response to the sulfonamides is variable, some seem to respond favorably though slowly, while in others the disease is influenced little or not at all. Influenza bacilli, at least the pathogenic strains, are probably not affected by the sulfonamides to any significant extent. They rarely cause primary pneumonia but may be important in cases complicating epidemic influenza.

**Choice of Sulfonamide Drugs**—*Sulfadiazine*, at the present time, is still the drug of choice in the treatment of pneumonias because of its range of effectiveness against the bacteria which cause pneumonia and because of its relatively low toxicity. *Sulfathiazole* is equally effective against the respiratory pathogens but it is considerably more toxic than sulfadiazine. In particular, nausea, vomiting, drug fever, skin eruptions and sensitizations are more frequent with the latter drug.

*Sulfamerazine*, the monomethyl derivative of sulfadiazine, is the most recent sulfonamide to be accepted for use in pneumonia. Its advantages are said to be its somewhat greater solubility, its more rapid absorption and slower excretion. The former property was considered likely to give rise to fewer renal complications, and the slower excretion should make possible the attainment of higher blood levels with small or less frequent doses. The slow excretion, however, is a disadvantage when untoward effects are encountered. From the reports

thus far available, the toxicity, including renal complications, even with the smaller doses that are recommended, have not been any less frequent than with sulfadiazine. Furthermore, the dosage originally recommended, namely, an initial dose of 3 gm followed by 1 gm every 8 hours for the average case, while giving blood levels comparable or sometimes even higher than with the usual and larger doses of sulfadiazine (4 gm initially and 1 gm every 4 hours) does not seem to give comparable clinical results. Higher and somewhat more effective levels are obtained with an initial 4-gm dose followed by 1 gm. every 6 hours. This dosage has been adopted as a routine for sulfamerazine in this clinic. With this dosage schedule the results seem to be comparable with those obtained from sulfadiazine. Because of the methyl group in sulfamerazine, the possibility of peripheral neuritis resulting from its use was anticipated on the basis of the experience with sulfamethylthiazole. From the clinical reports thus far available this has not proved to be the case.

*Sulfapyrazine* is another new sulfonamide compound that has proved highly effective in the pneumonias. This drug in clinical trials, has proved fully as effective as the ones already mentioned and toxic effects have been few. It is poorly absorbed from the gastro-intestinal tract and blood levels are low, being similar or even somewhat lower than with sulfathiazole. It has the disadvantage of being less soluble than the other drugs and the danger of urinary tract complications appears to be somewhat greater unless proper precautions are taken to insure an adequate urinary output.

*Dosage—Principle and Objectives*—It is well to bear in mind the principles on which sulfonamide dosage depends.

1. At the present time the most widely accepted theory of the mode of action of the sulfonamides is that they act by replacing essential metabolites which are indispensable to the growth and multiplication of the bacteria. This theory postulates a competition of the drugs with these metabolites. It would seem, therefore, that the maintenance of adequate drug levels at all times is essential.

2. Necrotic tissue and purulent exudates contain high concentrations of sulfonamide inhibiting substances. In their presence, therefore the sulfonamides may serve only to prevent the spread of infection to unaffected areas until there is healing or until the exudate is evacuated. In cases with such foci prolonged and intensive therapy may be necessary and dramatic results are not to be expected.

3. When continuously exposed to concentrations of drug which are below the effective bacteriostatic levels, bacteria tend to develop resistance or "fastness" to the drugs. Restart strains then require much larger concentrations of the drug, sometimes exceeding minimum toxic limits if the infection is to be influenced. It is best to attain a high concentration rapidly and to maintain it until the desired therapeutic effect is obtained.

4 After oral administration, there is a lapse of 2 to 6 hours before the maximum absorption of any given dose has occurred and the highest blood level attained. After this interval, the blood level drops progressively.

5 Maximum blood levels may be attained immediately after intravenous injection of the soluble sodium salts of the sulfonamide drugs, and very soon after their injection subcutaneously. These levels, however, decline more rapidly after the parenteral than after the oral injections because of more rapid excretion when the parenteral routes are used. The more rapid excretion, furthermore, increases the chances of producing crystalluria and the urinary tract complication that follows, unless proper precautions are taken to insure an adequate output of urine.

6 Blood levels are determined by the ratio between the rate of absorption and the rate of excretion and the maintenance of adequate levels depends on giving repeated doses at regular intervals. These intervals may vary somewhat according to the drug used, the state of hydration and the fluid balance.

*Routine Dosage*—The oral route of administration is the most desirable for all except a small percentage of cases. By this route wide fluctuations in blood levels are most easily avoided and urinary tract complications are probably minimized. For each of the drugs mentioned, except sulfamerazine, the same routine dosage orally has proved adequate and optimum for the average adult case of pneumonia, namely, an initial dose of 4 gm (or 2 doses of 2 gm given 2 hours apart) followed by 1 gm every 4 hours, day and night. With sulfamerazine, the same initial dose followed by 1 gm every 6 hours gives the best results according to the experience in this clinic. Others have obtained favorable results with 3 gm of sulfamerazine as the initial dose and 1 gm every 8 hours.

*Fluids*—All of the effective sulfonamides in both the free and acetylated forms are only very sparingly soluble in water and in urine. Since the drugs are concentrated by the kidney during the process of excretion, high levels of free and conjugated drugs are to be found in the urine. These may easily exceed the limits of solubility, and crystallization with resulting hematuria, oliguria, or even anuria may result. This may be avoided chiefly by giving enough fluids to insure an adequate output of urine. Usually an output of about 1200 cc daily is adequate to prevent this complication, but a somewhat greater amount is, of course, desirable. Since there is usually fever and sweating, it will require an intake of 2500 to 3000 cc daily to achieve this output. Parenteral administration of fluids such as physiological saline or 5 per cent glucose in water should be given if the patient does not take enough fluids orally or if the output is inadequate.

*Administration of Alkalies*—Both the free and acetylated forms of each of the effective sulfonamide drugs are more soluble in water or

urine that is alkaline than they are in an acid medium. A number of observers have noted also that in patients under treatment with these drugs, crystalluria is less frequent when the urine is neutral or alkaline than when it is acid. They have reported, also, that hematuria, oliguria, renal colic and anuria resulting from crystalluria are less frequent if the urine is kept alkaline. Since ordinarily the reaction of the urine in most cases of pneumonia treated with sulfonamides is acid, adjuvant alkaline therapy is advocated. This can be given in the form of sodium bicarbonate orally or as one-sixth molar solution of sodium lactate intravenously. Daily amounts of about 15 to 20 gm of the former and 1500 to 2000 cc of the latter are usually necessary to maintain adequate alkalinity of the urine.

These amounts of sodium, however, may result in the retention of water, particularly in patients with cardiac, renal or liver dysfunction. In addition, they may result in somewhat increased excretion of the drug which, in turn, may make it necessary to increase the dose in order to maintain effective levels. The combination of increased excretion of drug and retention of water may precipitate crystalluria and bring about just these urinary tract complications which it is desired to prevent. This condition may be overcome by the substitution of potassium salts (either as the bicarbonate, acetate or citrate) for all or for part of the sodium salts. Potassium salts used in this manner may act as a diuretic. The only danger from potassium is the possibility of producing serious cardiac arrhythmias, but these apparently occur only in patients with marked oliguria accompanied by nitrogen retention. Potassium salts should, therefore, be avoided in such cases.

**Parenteral Administration—Indications**—When it is desired to achieve a high blood level rapidly, as in severely ill patients, the initial dose of sulfonamide may be given parenterally as a solution of the sodium salt. This may also be desirable or necessary in patients who are vomiting and cannot retain the drug when given orally, in patients who are comatose or delirious, or after abdominal operations when the patient cannot take the drug by mouth. In other patients, due to difficulties in absorption or for other reasons, adequate levels occasionally cannot be obtained from oral doses alone and supplemental doses parenterally may be necessary.

**Procedure**—The soluble sodium salts of the sulfonamides may be given either (1) in the form of 5 per cent solutions in distilled water intravenously or (2) in concentrations of 0.5 to 1 per cent in isotonic saline, either intravenously or subcutaneous.

treatment in severely ill patients who may be dehydrated because they have perspired or vomit a great deal and have taken very little fluids, it is essential to precede any intravenous sulfonamide therapy with the administration of a sufficient quantity of fluid, preferably by giving 1000 to 1500 cc of physiological saline intravenously. The drug may then be given in dilute solution, as already indicated, and thus additional fluids provided which serves to restore proper hydration and thus to minimize the danger of renal complications.

**Dosage**—The average initial dose of drug for parenteral use is 5 gm. Larger amounts may be given up to an amount equivalent to 0.1 gm per kilogram of body weight. It is desirable to change to oral therapy as soon as feasible, giving the usual maintenance dose. If additional parenteral therapy is necessary, however, doses of 2 to 3 gm may be given at intervals of 8 to 12 hours, respectively, except where sulfamerazine is used when 2 gm are given every 12 hours. These amounts may be given in 250 cc, or preferably larger volumes, of saline intravenously or subcutaneously.

**Duration of Therapy**—In uncomplicated cases of pneumococcal pneumonia, sulfonamide drugs are given until the symptoms of the acute disease subside and the temperature, pulse, and leukocyte count have returned to normal and remained essentially so for 48 to 72 hours. In streptococcal pneumonias the latter period may be extended for 2 or 3 additional days. In staphylococcal pneumonias which are characteristically associated with multiple abscesses in the lung, treatment should be continued for one to three weeks depending on the extent of the damage to the lung and the response to treatment. Friedlander's bacillus pneumonias may also require prolonged and intensive therapy for the same reason. Where purulent complications are present or suspected, treatment may be continued for several days longer until these clear or until they are treated surgically. Some experienced clinicians prefer to reduce the dose to 1 gm every 6 hours after the temperature reaches normal but we prefer to continue with full doses and then to stop abruptly.

**Change of Therapy**.—When prolonged administration of sulfonamides is necessary, it is sometimes difficult to differentiate between drug fever and the persistence of fever due to infection or to pyogenic complications. When the fever is accompanied by the development of a rash it may be assumed to be due wholly or in part, to the drug. In this situation, it is best to discontinue sulfonamide therapy, but if further chemotherapy seems desirable a change to another sulfonamide is indicated. It is important to emphasize in the connection that sulfadiazine and sulfamerazine usually act in the same way with respect to drug fever and rashes and, therefore, cannot be substituted for one another under these conditions. Sulfathiazole or sulfapyrazine may be used, or even sulfapyridine, if that happens to be the only drug to which the patient is not sensitive or the only other drug available.

Better still, penicillin may be used unless one is dealing with a Friedländer or influenza bacillus infection. Crystalluria, even when accompanied by hematuria, does not warrant cessation of sulfonamide therapy. Additional fluids, preferably by the intravenous route, and alkalis, best given as sodium lactate parenterally, are indicated. Subsequent dosage will depend on the need for further treatment, on the blood level and on the possibility of maintaining a proper urine output.

**Drug Levels.**—It is desirable, for the most effective management of sulfonamide therapy, to determine the blood level two or three times weekly during the course of treatment. This is indispensable in patients in whom there is known or suspected impairment of renal function, particularly in old persons and in those with hypertension of long standing. In such cases even more frequent determinations may be indicated for the conduct of therapy in order to avoid excessive retention of the drugs. It is also essential to know the blood level whenever the response of the patients seems inadequate.

The usual blood levels obtained with the routine dosage and hydration regimen are 6 to 10 mg per 100 cc for sulfadiazine, similar or slightly higher levels for sulfamerazine and 4 to 8 mg with sulfathiazole. The levels for sulfapyrazine are even lower than for sulfathiazole. All of these levels (of free drug) are usually adequate for most cases of pneumococcal or streptococcal pneumonias but slightly higher levels are desirable in staphylococcal and Friedländer's bacillus pneumonias. Very high and even dangerous levels are rapidly attained if renal function is impaired. In such cases, excretion is slow and the amount of acetylated drug (which is ineffective therapeutically) increases progressively. On the other hand, levels will be low and adequate concentrations difficult to maintain if fluid administration is excessive and large doses of alkalis are given.

**Failures of Sulfonamide Therapy.**—Failures may still be expected (1) in cases in which treatment is begun late in the disease after much of the damage from the infection has been done, (2) in very old patients or patients with severe underlying systemic disease, (3) when insufficient attention is given to the general aspects of therapy, such as the treatment of cyanosis with oxygen, the management of incipient or manifest congestive failure and pulmonary edema, (4) where care has not been taken to avoid the development of renal complications or to take the necessary precautions in cases in which renal function is already impaired, (5) when treatment is inadequate either because the total dose is too small, the interval between individual doses is too long, or the treatment is interrupted or discontinued too soon, (6) when focal purulent infections are present and inadequately treated, (7) when the organism causing the disease is resistant to sulfonamide drugs or becomes resistant during the course of the treatment and before recovery has taken place, (8) in cases of errors in diagnosis when the chief cause of the pulmonary disease is either some other

terial agent or a bacterial agent which is not affected by the sulfonamides

The possibilities of avoiding some of these failures or for properly managing them when possible are often obvious provided that the causes are recognized. The development of resistant strains is probably minimized by intensive treatment from the start and particularly by avoiding the use of small "prophylactic" doses over long periods in the management of simple upper respiratory tract infections. Changes from one sulfonamide drug to another are only rarely helpful in such cases. Type-specific antipneumococcus serum is useful in such cases when the pneumococcus is the inciting agent. At present, penicillin is the treatment of choice when drug-resistant infection is encountered. Focal purulent infections are best treated by surgical drainage where it is feasible and can be instituted at the proper time. Treatment with sulfonamides, maintained while empyemas are drained intermittently by thoracentesis, may result in a few cures without surgical intervention. Penicillin may be injected after such thoracentesis and may increase the chances of such cures. Care to avoid renal complications by proper fluid and alkali intakes and the precautions necessary during the treatment of patients who have kidney damage have already been mentioned.

### PENICILLIN

There is now available for general use a supply of penicillin which, though limited, should be adequate if reserved for use in those infections in which it has been shown to be particularly effective and superior to other available agents. The organisms which are important pathogens in pneumonia and are susceptible to penicillin include all types of the pneumococcus, hemolytic streptococcus, *Staphylococcus aureus* and *Streptococcus viridans*. Most pneumococci and hemolytic streptococci are highly susceptible, but strains of *staphylococcus* and *Streptococcus viridans* vary considerably in their sensitiveness to the action of penicillin. The influenza bacillus and Friedlander's bacillus are almost entirely resistant to its action. Indeed, Fleming has successfully employed penicillin as a means of obtaining almost pure cultures of influenza bacilli from sputum, throat cultures and other materials which contain a mixed respiratory flora.

Experiences with penicillin in pneumonia are quite limited, since its greatest uses have been in other fields. From the observations of Tillet and others and from more recent studies in this clinic, coupled with the accumulated published observations on the use of penicillin, it is possible to outline tentatively some of the details concerning the use of penicillin in the pneumonias. The general principles of the use of penicillin are enumerated elsewhere in this issue by Dr. Keefer and these should become familiar to all who propose to use this new agent.

**Indications**—Penicillin like the sulfonamides should be used only in

cases in which susceptible bacteria are causing infection. Bacteriological diagnosis is, therefore, important here, too. Blood cultures and sputum for bacteriological examinations should be obtained before treatment is started, since it may be difficult or impossible to obtain a positive culture after treatment has been given. Penicillin should be used primarily in cases of pneumococcus, streptococcus or staphylococcus pneumonias but it may be used in cases in which these organisms are present in moderate to large numbers in sputum even though the primary disease may be due to a virus or to some other organism. In the latter cases, the primary disease will not be influenced, but benefit may be derived from the elimination of these secondary invaders.

Penicillin is now the treatment of choice and should be used from the start, in cases of pneumonia, under the following conditions:

- 1 Where the patient is in *extremis* or in shock. In such cases penicillin is preferable because it acts more rapidly than sulfonamides and without the toxic effects encountered from the latter.
- 2 In patients who have impaired renal function.
- 3 In patients with congestive heart failure or ascites and edema resulting from liver damage. Patients with impaired renal function and those who have a tendency to retain water handle sulfonamide drugs poorly. They require great care to avoid further renal damage when such drugs are used because of the difficulty of maintaining an adequate urinary output. This condition, on the other hand, is favorable to penicillin therapy since it is easier to maintain effective levels in the blood when the urinary output is low.
- 4 In cases of staphylococcus pneumonia. Most strains of staphylococcus are much more susceptible to penicillin than to the sulfonamide drugs.
- 5 In patients who are known to be sensitive to the sulfonamide drugs and who have severe reactions (fever, rashes, nausea and vomiting) early in the course of treatment with these drugs.

A change to penicillin from sulfonamide therapy is indicated in the following situations:

- 1 When there is a failure to respond to adequate doses of the sulfonamide drugs as evidenced by (a) persistent bacteremia after 24 hours or more of treatment in spite of adequate sulfonamide levels in the blood, (b) significant increase in the number of bacteria in the sputum (as seen by direct smears) under the same conditions, (c) extension of the pulmonary lesion, (d) lack of improvement in the acute symptoms, or failure of the temperature and pulse to drop significantly in 36 to 48 hours. When renal complications, particularly oliguria, nitrogen retention or anuria occur before the patient's pneumonia has cleared, crystalluria even with slight microscopic hematuria may be



overcome by increasing the fluid intake and by administration of alkalis, as already noted. This alone should not necessarily indicate a change to penicillin.

- 3 The occurrence of other drug reactions such as fever, rash and acute hemolytic anemia early in the course of treatment or before the disease has been adequately controlled.
- + Penicillin may be used locally when infected pleural fluid or other accessible foci of infection develop. Under these conditions, treatment with the sulfonamides orally may be continued until the infection is well focalized.

**Dosage**—Some investigators have obtained satisfactory results in cases of pneumococcal pneumonia with comparatively small doses of penicillin given over a short time. The use of these small doses was prompted at first by the limited supply. Experience in this clinic suggests, however, that more intensive and somewhat more prolonged therapy is usually necessary, particularly in severe cases, in order to obtain the optimum therapeutic effect without relapse. The following schedule of dosage has been found satisfactory and is suggested tentatively until more experience is accumulated. In very severe cases, an initial dose of 10,000 to 20,000 units may be given intravenously in a small amount of sterile saline (10 to 50 cc). All subsequent doses are given intramuscularly, the first one being given directly after the completion of the intravenous dose.

For *pneumococcal* and *hemolytic streptococcal pneumonias* 15,000 units every 2 hours for two to four doses then every 3 hours until 12 hours after the temperature has become essentially normal and the acute symptoms have markedly improved. After that time, the dose is reduced to 10,000 units every 3 hours and continued for another 24 to 48 hours depending on the initial severity and the character of the response. In general, the more severe cases and those who seem to respond slowly should be given larger doses at shorter intervals and the treatment kept up longer.

For *staphylococcal pneumonia*, larger doses are needed and treatment should be kept up longer than in pneumococcal or streptococcal pneumonias. This is necessitated by the fact that staphylococci, in general, are less sensitive to penicillin than are pneumococci and streptococci. Furthermore, there are greater strain differences among the staphylococci. It may be necessary to increase the individual doses or decrease the interval between doses if the response is slow or inadequate. It must also be borne in mind that the staphylococcus characteristically produces multiple abscesses in the lung, and empyema often occurs early. Since the penicillin does not penetrate into the pleura or into the abscesses after they have become established, prolonged treatment is necessary to localize the infection. The penicillin must be placed directly into the larger purulent foci if one should attempt to influence them without surgical drainage. The average adult case

of staphylococcal pneumonia of moderate severity should receive 20,000 to 25,000 units (in 4 or 5 cc of saline) every 2 hours for 24 to 48 hours and then every 3 hours for 7 to 14 days.

For the treatment of empyema caused by any of the susceptible organisms, the pleural cavity must be aspirated every 24 to 48 hours and 25,000 to 40,000 units (in 25 to 40 cc of saline) injected into the cavity after each aspiration, the dose depending on the size of the empyema. This treatment should be continued until the fluid remains sterile and the cavity is closed or until surgical drainage is instituted. In our experience most cases of empyema have eventually required surgical drainage although some observers have reported a high percentage of cures from penicillin alone. Tillett has suggested lavage of the pleural cavity with sterile saline after each aspiration and before each penicillin injection. This procedure may increase the chances of success.

#### USE OF SULFONAMIDES AND PENICILLIN IN INFLUENZA AND VIRUS PNEUMONIAS

There is no evidence to indicate that either sulfonamide drugs or penicillin has any effect on virus diseases of the respiratory tract. Influenza and virus pneumonias, however, may be complicated by bacterial infections and these secondary infections may be serious. They account for a large majority if not all of the fatalities from influenza and probably also from primary pneumonias which are of known or of suspected viral etiology. When the presence of such bacterial infections is recognized or suspected, early and intensive antibacterial therapy is indicated. Their presence is detected by the purulent character of the sputum and the finding of the pathogenic bacteria in significant numbers in direct smears or cultures of the sputum. The course and character of the disease are also usually modified perceptibly when pulmonary infection with such bacteria occurs.

In influenza, patients who are acutely ill with high fever and marked prostration are the ones most likely to develop bacterial pulmonary complications and should be observed carefully with this in view. Preternatural pain, cough, purulent sputum, leukocytosis and signs of bronchitis or of consolidation should be taken as evidence of such complications and as indications for treatment. Recently staphylococcal pneumonias have been seen with unusual frequency as a complication of influenza. In view of the seriousness of all such pneumonias when they occur during or immediately following an attack of influenza, the need for early and intensive treatment is obvious.

The significant findings in such a case which was treated with penicillin is shown in Figure #2. In this case the disease was early and was kept more or less localized to the left lower lobe. Although some fluid developed, this cleared up without drainage of the pleural space. Because of the peritesticle of pneumonia in the lar-

longed treatment was necessary and was, therefore, maintained for 2 weeks after the fever subsided

Cases of *primary atypical pneumonia*, the so-called "virus" pneumonias, have been observed in large numbers in military personnel as well as in schools and colleges, and some outbreaks have been described among hospital personnel. There have also been appreciable numbers

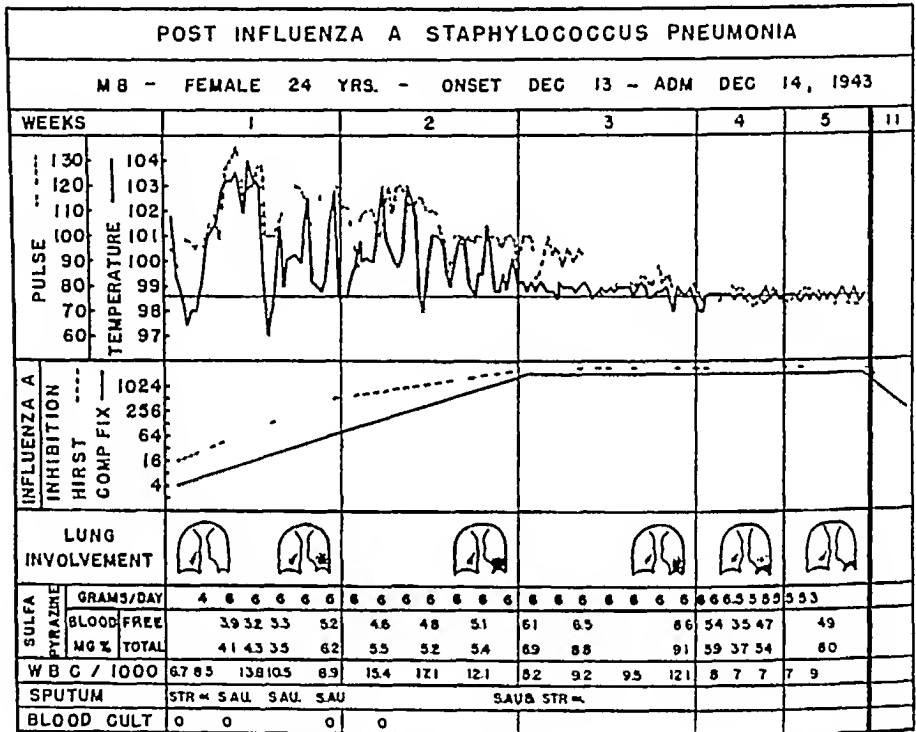


Fig 82—Relevant findings in a case of staphylococcal pneumonia which developed in a patient with clinical influenza. Influenza A virus was isolated from throat washings at the time of admission and antibodies for this virus later developed. After temporary improvement, fever recurred with elevated pulse rate, cough, presternal and some pleuritic pain. Sputum was scant at first and later became somewhat more copious and purulent in character and hemolytic staphylococci in moderate to large numbers were obtained in cultures. The patient was acutely ill for 10 days after which improvement was steady. There were signs of bronchitis and then signs of consolidation in the left lower lobe. X-ray findings suggesting cavitation and a small amount of pleural fluid appeared in the second week but these cleared gradually. The lungs later showed complete clearing.

of cases in the general population reported from different parts of this country. While bacterial infections complicating such cases have been surprisingly few, some of those which have occurred have been quite serious and have contributed in appreciable measure to the outcome in the few fatalities that have occurred from this disease. In this clinic, the hemolytic streptococcus and *Staphylococcus aureus*, particularly the latter, have been the chief offenders, although pneumococci have



duced severe secondary infection in the lungs is shown in Figure 83. This was a typical severe case of widespread primary atypical pneumonia of unknown etiology. The staphylococcal infection was first noted at the end of the second week in the hospital at a time when the patient was apparently recovering from the primary disease. The development of a high titer of cold agglutinins in the patient's blood, as well as the development of agglutinins for *Streptococcus* 344 of Thomas and his associates are confirmatory evidence for the diagnosis of primary atypical pneumonia. There was little doubt in the minds of those who observed this case that the antibacterial therapy was responsible for the eventual recovery of this patient.

#### SPECIFIC ANTISERUMS

Before penicillin became available, type-specific antipneumococcus serums were indicated for most of the cases of pneumococcal pneumonia in which penicillin is now recommended (see above). The latter agent has the advantage of greater simplicity of administration and almost complete absence of untoward reactions. When specific antipneumococcus serums are used, it is important to take all of the usual precautions which are indicated for the intravenous injections of foreign serums in order to minimize the unfavorable side effects.

#### COMMENT

It is not possible at this time to compare, with any great sense of finality, the relative values of the sulfonamides and penicillin in the treatment of the pneumonias. Both types of therapy are highly effective against the pneumonias caused by the common bacterial agents, and are not effective against respiratory infections caused by viruses. The sulfonamides have the disadvantage that they do produce untoward reactions in an appreciable number of cases and particularly in certain types of cases, require considerable vigilance and intelligent use. This, however, does not detract from their very wide usefulness and, in general, their simplicity of administration.

Penicillin has one disadvantage in common with the sulfonamides, namely the fact that the doses must be given repeatedly and at frequent intervals. The rapid rate of excretion of penicillin makes it even more important with this agent than with sulfonamides. In addition, every dose of penicillin must be injected, and this is a not inconsiderable disadvantage. To be sure, this agent may be given by continuous intravenous injection, but that requires constant supervision and has serious disadvantages in itself. These disadvantages, however, are offset by the almost complete absence of untoward effects from penicillin.

An attempt was made in this paper to call attention to some of the outstanding features of the two most important types of therapy that are now available, insofar as they apply to the treatment of the pneu-

monias The indications for their use and practical aspects of their management are outlined as far as present experience permits Further experience will undoubtedly occasion modifications of the opinions and recommendations that have been presented

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# OBSERVATIONS ON FOUR PATIENTS WITH SEVERE ASTHMA

## The Need for Special Treatment

FRANCIS M. RACKEMANN, M.D., F.A.C.P.\*

WHEN the symptom "asthma" becomes severe and finally gets out of control so that the patient is no longer relieved by epinephrine injected under his skin, or by doses of aminophylline injected into his vein, the situation may become dangerous. Aside from the asthma itself, these patients are utterly miserable. They are weak, they are exhausted, and they almost plead for some medicine to make them sleep and give them rest. In many cases this exhaustion with the slight cyanosis, the sweating, the cold clammy skin, the inability to eat or drink and the obvious misery make a symptom picture that appears more important than the difficulty in breathing. When the picture develops suddenly, the patient goes into a state of collapse, his condition simulates a sort of surgical shock.

Last March, I<sup>1</sup> discussed certain new theories concerning asthma and used as a text one of the cases reviewed here. The general disturbance of the whole body was described, and some evidence was presented that the trouble was due probably to a disturbance in the function of the adrenal glands. The conception of Selye<sup>2</sup> that severe injuries or insults of various varieties can cause an "alarm reaction" with its shock and counter-shock phases was mentioned.

In this clinic I would like to present 4 rather typical patients and to discuss the lessons which their study provides and then to comment on what can be done about it in the way of treatment. In the first 3 of these patients the collapse was sudden and acute—the condition was alarming and dangerous. In the first case the patient died during bronchoscopy.

### Case I Intrinsic Asthma with Collapse Presumably Due to a Disturbance Comparable to the Alarm Reaction of Selye

Miss K. G. C., a woman of 50, was first seen in September, 1943. In the preceding March she had had shingles in the area supplied by the left ulnar nerve, and a month later, in April, came the first asthma attack of moderate severity which lasted for about a month. During the early summer she improved, but in August came asthma again and this asthma continued until the time of her visit.

The patient was a large, well built woman of 50, who weighed 145 pounds. She was quite short of breath as she came in but became more comfortable on sitting by the desk. Her pulse was rapid (about 100), the blood pressure was up

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From the Allergy Clinic of the Massachusetts General Hospital.

\*Lecturer in Medicine, Harvard Medical School, Physician, Massachusetts General Hospital.

to 160/90. Her lungs contained numerous dry wheezy rales, but the breath sounds were of fair quality and showed no evidence of any local process in the lungs. Skin tests were made to about twenty different substances by the intradermal method but the results were negative except for a very slight reaction to house dust. Her white blood cell count was 12,000, with eosinophils of 9 per cent.

The patient was given a diet called "Eat Nothing But" which limited her menu to a few well chosen items and which at the same time reduced her intake of sugar and starch. She was advised to take a level teaspoonful of extra salt with each meal, she was given potassium iodide (10 drops after meals) and tablets of an ephedrine mixture (ephedrine 0.024 gm [ $\frac{3}{8}$  grain] aminophylline 0.1 gm. [ $\frac{1}{2}$  grains] and phenobarbital 0.008 gm [ $\frac{1}{8}$  grain]) to be taken at bedtime. Finally vaccines were prescribed in weekly doses and it was encouraging to find that these vaccines produced local reactions sometimes as large as an egg and often made the asthma worse—encouraging because as soon as the size of the dose was reduced, she improved.

In early December, however the asthma became worse again, and at that point the patient was admitted to the hospital. During the first three nights she needed aminophylline intravenously and three or four doses of adrenalin a day, but later she unproved to some extent. However the asthma did not clear as it does in the typical extrinsic cases, the wheeze recurred every night. In general, she was tired and apathetic—she was not doing well. X ray of the chest showed the diaphragms smooth in outline but limited in motion. The upper lung fields were quite clear, but the lung markings were increased in the lower lobe. In the lateral view the increase in the markings appeared to involve the right middle lobe, "which may be a little reduced in size." The heart and aorta were normal in appearance. The mediastinum was not displaced.

At the end of a week in the hospital, bronchoscopy was advised and for two reasons. First, the sudden onset of asthma at age 50 in a woman who had always been healthy suggested the development of a local lesion such as a bronchial tumor. And then, second, it seemed possible that during the procedure of bronchoscopy it might be possible to remove the sticky mucus from her tubes by suction and so relieve her symptoms.



was injected with a long needle into the heart, a special oxygen apparatus to make positive pressure through a special short bronchoscope was applied, but it was too late, the heart had stopped beating, she was dead

At autopsy the lungs were voluminous and distended. They had a pale grayish blue color. They did not collapse on standing. The large airways were clear except for a little thin mucus in the lumen, but cross-section showed each of the smaller bronchi to be entirely filled with tough, sticky secretion which could be grasped with a forceps and pulled out. The heart weighed 300 gm and was essentially normal. The other organs were normal. Death was evidently due to asthma.

*Comment*—Why did the end come so suddenly when up to that time the patient seemed to be doing well? The blood pressure was a little high before the operation. Unfortunately it was not taken during the procedure. No doubt the pressure fell abruptly. At autopsy there was no gross evidence of disease in the heart or kidneys. The coronary vessels were quite within normal limits. On the other hand, P D White<sup>3</sup> states "There may or may not be any evidence of cardiovascular pathology in angina pectoris." One of the pathologists who saw the autopsy believed that she died of coronary spasm but if this is so it is hard to prove. The sticky plugs which occluded all of the medium sized bronchi and prevented the air from entering the terminal alveoli were easy to see and justify the conclusion that the patient suffocated from asthma.

This patient's asthma was of the intrinsic type. It did not begin until age 50 and from the onset was progressive in severity. Skin tests were negative, which was not at all surprising since there was no clinical evidence of any allergy to dusts or to foods. The ups and downs in the disease bore no relation to changes in season or environment. She did not have allergy in any ordinary sense. An allergy to drugs is, however, a possibility. She had received no morphine but she was given a dose of nembutal by mouth and cocaine was applied pretty generously to her throat and bronchi. Other patients sensitive to aspirin have developed violent asthma after being given a single 0.33 gm (5-grain) pill of aspirin. Perhaps she, in the same way, was sensitive to barbiturate or to cocaine. Unfortunately there is no way in which this idea can be proved or disproved.

During all her illness the patient was apprehensive, frightened by the disease. Although no observations were made on her adrenal function or even of her electrolyte balances, it is fair to compare her case with others and suggest that a disturbance comparable to the alarm reaction of Selye played at least a part in her collapse.

#### Case II Asthma of Extrinsic Origin with Collapse Presumably Due to Too Much Adrenalin

Mr R. A. R., a busy salesman, had been well all his life until the age of 50 when in the month of March he developed a bad cold which did not clear and left him with a stuffy nose which continued all through the spring,

summer and fall. In early December his appendix was removed and the clue to the diagnosis was the fact that in the hospital after the operation his nasal symptoms disappeared, he could smell once more. Back at home he stayed well for several weeks but gradually his nasal symptoms returned. During the second summer a secondary operation was made for a hernia in the scar. This time in the hospital his nose did not clear, the stuffiness continued through the rest of the summer and through the second fall. In November (age 51), the first asthma came and a month later he applied for treatment. He was still an active business man who in general appeared quite well. He had a remarkably stuffy nose, with red swollen membranes and a large polyp filling the left nasal cavity. X ray showed all the sinuses dark, blood smear showed 10 per cent eosinophils in a white count of about 12,000. Skin tests made by the intradermal method revealed a small reaction to ragweed and positive test to dog hair extract.

The family dog was sent away for a trial period and when the man was seen again in December he was very much better, his nose was clear with no stuffiness, he could smell normally. Meantime the nasal polyp had been removed but no other operation had been made on the nose or sinuses.

In the following February his wife drove the car to the kennel so as to get the dog and deliver him to a friend. Three days later the patient (age 52) drove the same car to an out-of-town appointment and during the next few days he drove it a good deal. Asthma returned and each night it increased in severity. Meantime he was given adrenalin and also a syringe and the wife was advised to inject adrenalin as often as might be necessary to relieve the symptoms. Being faithful and conscientious she did this but unfortunately she overdid it for on the tenth day of the attack she telephoned to say that the adrenalin was no longer effective.

and his nose would become stuffy but then he soon bought a new car and no symptoms in nose or chest have since occurred. He has had no further contacts with dogs.

*Comment*—In spite of the late age of onset, and the rather typical story of chronic vasomotor rhinitis leading to asthma, the diagnosis of extrinsic asthma due to a sensitiveness to dogs seems well established. The dreadful episode of collapse was dramatic indeed. It was caused in the first place probably by fatigue or anxiety due to asthma, or perhaps by a new infection which complicated the asthma. The exact cause is unknown. The acute episode was precipitated by too much adrenalin. The clinical picture was that of a profound collapse. As he sat in my car the man was in a state of "surgical shock." At that time the general shocklike symptoms were much more important than the difficulty in breathing and the wheeze. Incidentally I gave him a dose of morphine which nowadays is "against the rules" since in uncomplicated asthma, morphine is a dangerous drug. In this particular situation, however, its use was justified. The dose did the patient good because the symptoms were due to shock and not to asthma.

### Case III Asthma and Collapse Both Due to an Acute Infection

Mr. L. S., an Italian laborer, aged 63, had had attacks of severe asthma off and on since the age of 38. These were brought on by new colds and occurred two or three times during each winter. The last attack began 3 days before the period of observation and when seen at home the man was in desperate straits. He was sitting on the side of his bed, gasping for breath. He was cyanotic, he was sweating, he was exhausted and miserable. His pulse was full and rapid, his blood pressure 130/80. He had been given adrenalin before without results and now adrenalin was unsuccessfully given again and again. An ampule of aminophylline containing 240 mg. in 10 cc. of fluid was injected intravenously without much benefit.

As in the second case (*vide supra*) it was decided to take the patient to the hospital for further treatment, so he was carried downstairs and into the car. Upon his arrival in the emergency ward an intravenous drip injection of 5 per cent glucose in saline was started immediately and in 20 minutes he was rather better. The next morning he was in an oxygen tent, the intravenous drip was still running, but now with glucose 5 per cent in water instead of in saline. He was desperately ill. An area of bronchial breathing was heard in the left chest with a friction rub over it. The white count was 16,000. The diagnosis of pneumonia was made and appropriate treatment was started, but 10 hours later the patient died. Unfortunately an autopsy was not obtained.

*Comment*—When first seen the man presented the same appearance of shock as did the second patient, but in this case the immediate cause was a severe infection, the shock was of toxic origin. In the final picture, the element of asthma was unimportant.

### Case IV "Countershock" Producing Symptoms More Important Than the Causative Asthma

Mr. E. S. T. was a lawyer, aged 52, whose case was the one referred to in the previous paper.<sup>1</sup> All his life this man had been subject to head-colds

and what he called "nasal catarrh." At age 47 this catarrh increased so that a stuffy nose became quite troublesome. At about the same time the patient developed a cough which came mostly at night and was occasionally accompanied by a slight wheeze. He was sent to Arkansas for a rest and treatment and it was while there that the first real asthma occurred. After that and for the next 5 years this asthma was practically continuous throughout both summer and winter. New head colds would make the asthma worse. He had had all manner of treatment—intravenous injections of neoarsphenamine, and intrabronchial injections of lipiodol as a treatment for supposed bronchiectasis. He had been sent to Arizona and to many different hospitals but with no real improvement at any time. The asthma continued in many different places and under many different conditions of atmosphere and weather. He had had three operations on his nose. At age 51 nasal polyps were removed and a few days later the sinuses were attacked. On the next morning he was found on his hospital bed unconscious and blue. Fortunately an excellent internist made a prompt diagnosis of meningitis and treated him immediately with sulfa drugs in large quantities so that after a few terrible days he recovered.

Once again the patient was sent to Arizona but the asthma grew worse instead of better. A doctor enthusiastic about allergy took away his food and allowed nothing but fruit juices and gelatin with several enemas a day—"the treatment almost killed me." A little later a third operation was made on his nose and this time the results were better for his nasal symptoms became much less troublesome. At another good hospital it was recognized that "One of the most important aggravating factors has been his nervous tension. While in the hospital he has been relaxing perfectly and is having very little trouble with his asthma. He sleeps most of the night without coughing. He is instructed to avoid exertion and overwork and anything which will upset him in a nervous way. The prognosis is guarded because of the emphysema."

important, the general theory concerning the nature of the process was explained to the patient and this alone gave him new courage and something tangible to work on. Unfortunately he lived at a distance so that after discharge from the hospital here he was not seen again. Letters, however, were encouraging, even enthusiastic about his improvement. During the following 2 months he gained 8 pounds in weight.

It was very unfortunate and very disappointing to everyone who knew this man that he died quite suddenly about 5 months after the start of his treatment. He died in a violent attack of asthma which was really the first severe attack that he had had since the start of treatment.

*Comment*—This man had two sets of symptoms: the asthma itself was obviously dependent upon emphysema with excessive mucus in the tubes, but even so there was no good evidence of the presence of permanent irreversible lesion; there were times when he could sit comfortably in a chair or could even lie quite flat in a bed, just as there were times when he could walk down the hospital corridor to the toilet. The second symptoms were more interesting, the loss of weight, the debility, the fatigue and the anxiety constituted a picture which was quite separate from this asthma. This man was in a state of chronic exhaustion—comparable perhaps to the countershock phase of the alarm reaction which Selye has described. As time went on, it became clear that treatment on this new basis was quite worth while. The patient's death was most unfortunate and very disappointing, as stated.

#### DISCUSSION

It is quite interesting to compare these four cases. Each was quite dramatic and each presented the element of shock, less acute in Case IV than in the others. In other respects, however, the pathological pictures were quite different.

In Case I the shock was due presumably to a vasomotor collapse dependent chiefly on apprehension and fright. It was a nervous collapse caused by the bronchoscopy. One thinks of drug allergy, of spasm of the coronary arteries, or possibly of some injury to important structures caused by the operation, but there was no evidence to support these theories. The shock was secondary to the asthma and the bronchoscopy. In Case II, the asthma was of extrinsic origin—an allergy to dogs—but the shock was due presumably to too much adrenalin. In Case III, the asthma and the collapse were both due to an acute infection. In Case IV there was no actual shock; the patient was in the phase of "countershock," but the point is that this condition was much more important than the asthma which produced it.

The alarm reaction is a general reactive pattern that develops after injuries. Immediately after trauma or excitement of almost every kind, the adrenal gland puts out adrenin from its medulla. Also there is reason to think that secretions from the cortex are modified at the same time. In his Harvey Lecture on Cushing's syndrome, Albright<sup>4</sup> presents the theory that the adrenal cortex develops among other

things, an "S" hormone which is concerned with the metabolism of sugar and an "N" hormone which is concerned with the metabolism of nitrogen. In times of stress, as in the alarm reaction, the sugar hormone is increased to provide extra energy, whereas the nitrogen hormone is withheld so as to conserve the protein building materials of the body. Normally these changes are temporary and in a few days or weeks the hormones return to their normal proportions. If, however, the injury is repeated, the disturbance of hormones continues, and so gives rise to a difficult situation. More and more body protein is broken down to make sugar, and less and less protein is built up to repair the damage. This goes on until the debility becomes severe. This is the brief gist of the theory.

Treatment of the shock stage is the treatment of shock in general. The intravenous injection of fluid in large amounts (1000 to 2000 cc.) is indicated, and human plasma should be more effective than physiologic solutions of salt, or of sugar, or of both in water. Unfortunately plasma has not been tried by me for the treatment of shock in asthma. The patient should be kept as quiet and as comfortable as possible and given confidence by good nursing care. He ought to be in a hospital, but as the cases described above indicate, the move to the hospital may not be safe. In Cases II and III the patients almost died from extra exertion of the trip, but they both rallied promptly as soon as the hospital treatment was begun. The margin of safety was narrow and another time, it might be better to give the intravenous fluids at home and then move the patient later.

It is very tempting to advise morphine which evidently was of benefit in Case II. If the shock is worse than the asthma, morphine is probably justified, but if the asthma itself—the bronchospasm—is already severe, morphine may kill by depressing the respiratory center a trifle too much. 1 pinephrine may do harm.

comes more comfortable, then steps can be taken not only to find and treat the cause of the asthma but also to try and find why it was that the patient was so depleted that he reacted to the asthma in so severe a pattern. As for the theory of the "A" and the "N" hormones discussed by Albright, testosterone propionate is said to be a specific stimulant toward the building of body protein, and in theory at least it should be very useful in the treatment of this condition. It was evidently effective in Case IV.

The chief purpose of this paper has been to call attention to symptoms which may in the first instance develop because of the asthma but which may later continue and increase to make a condition far more serious than the asthma itself. To recognize that condition is important because it requires special treatment.

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## ADENOID BRONCHOSINUSITIS IN INFANTS AND CHILDREN

STEWART H. CLIFFORD, M.D.\* EDWARD B. D. NEUFELDER, M.D.†  
AND CHARLES F. FERGUSON, M.D.‡

ADENOID bronchosisinusitis in infants and children develops as a complication of upper respiratory infection. The infected adenoid tissue and nasal sinuses produce a purulent discharge that obstructs the nasal passages and descends into the trachea and bronchi. In time this postnasal dripping may penetrate the finer bronchi and set up a diffuse peribronchial infection.

Every practitioner is familiar with the chronic nature of this disease. Until the advent of chemotherapy little help could be afforded, beyond general supportive measures designed to tide the patient over until natural recovery took place. Attempts to treat this condition by chemotherapy alone have been disappointing. While the infection might be brought under temporary control, withdrawal of the drug and exposure to new infection would start a recurrence of the disease process. Our experience during the past few years gives promise that a large proportion of these patients, in whom the primary etiologic factor is chronic infection and hypertrophy of adenoid tissue, may be cured quickly by a combination of sulfonamide therapy and surgery.

### ETIOLOGY

There is included in this discussion only those patients whose adenoid bronchosisinusitis has developed as the direct result of infection. Those patients in whom bronchosisinusitis has occurred secondary to allergy or some anatomical variation in the nose or sinuses have been excluded.

The organisms usually found associated with adenoid bronchosisinusitis are the beta hemolytic streptococcus, the pneumococcus and the staphylococcus aureus. The presence of bacterial infection is further indicated by increased blood sedimentation rates and elevated white blood counts even in the periods between the exacerbations of the



Infection of the lymphoid tissue in the posterior nasopharynx may spread underneath the epithelium to the nasal sinuses. Hypertrophy of the adenoid tissue obstructs the posterior nasal cavity preventing adequate passage of air and normal drainage into the pharynx. This results in stagnation of nasal discharge and infection spreading into the nasal sinuses. The ethmoid cells and the maxillary sinuses, both of which are present at birth, are the paranasal sinuses with which we are primarily concerned in adenoid bronchosinusitis.<sup>1</sup> Following the infection of the sinuses the infection may travel to the dependent bronchi by a continuity of the mucous membrane surfaces, by gravity through the pharynx, larynx and trachea, and by way of the mediastinal lymphatics to the lung.<sup>2</sup>

### INCIDENCE

**Season**—It is of interest that nearly all of our patients with adenoid bronchosinusitis gave a history of having acquired their original upper respiratory infection in September, October or November. They all had had conservative treatment, usually several periods of sulfonamide therapy, for the succeeding two or three months. Practically all of the operations attempting to correct this condition were performed between December and March. After April 1 patients presenting this syndrome were rarely encountered.

**Age**—The age incidence of this condition is also of interest. Our patients were uniformly distributed between ages of 11 months and 8 years. There are at least three factors that may explain why patients with this condition are rarely seen after 8 years of age: (1) the development of individual immunity, (2) the relative increased size of the nasopharynx, and (3) the atrophy of lymphoid tissue that takes place generally after this age.

### SYMPTOMS AND COMPLICATIONS

The children suffering from adenoid bronchosinusitis give a history that they have never recovered fully following an original "cold" acquired some months before. There has been persistent nasal obstruction with mouth breathing and "snoring" at night. During the day there is apt to be profuse nasal discharge and at night the posterior dripping produces frequent paroxysms of coughing. The course of the disease is characterized by periods of relative improvement with a normal or slightly elevated temperature alternating with exacerbations of all symptoms and increased fever. The children are frequently in school one week and out of school for two or three weeks. The patients fail to gain or actually lose weight, they look poorly, their color is pale and they fatigue easily.

Patients with adenoid bronchosinusitis may develop numerous complicating infections during the course of the disease. Recurrent attacks of tonsillitis, cervical adenitis and otitis media are frequently encoun-

tered. More rarely, acute ethmoiditis, osteomyelitis, sinus thrombosis, mastoiditis and brain abscess may be encountered. The disease may incite attacks of asthma or produce a capillary bronchitis or pneumonia.

#### DIAGNOSIS

The presumptive diagnosis of adenoid bronchosinusitis can be made from a history of the symptoms recorded above. The positive diagnosis of this syndrome demands an x-ray examination of the pharynx, sinuses and lungs.

**Roentgen Diagnosis.**—In order to establish a roentgen diagnosis of adenoid bronchosinusitis it is necessary to have an adequate x-ray examination of the paranasal sinuses and nasopharynx, as well as film and fluoroscopic examination of the chest. The examination should

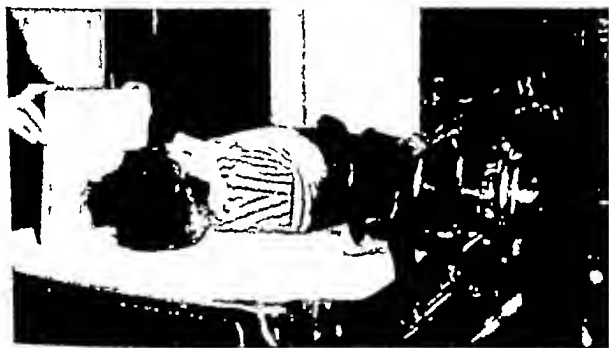


Fig. 84.—Patient in position for a lateral film of nasopharynx. The cassette should be supported by sandbags or held by a member of the patient's family.

through the nose. With a little practice it should be possible to obtain excellent films of the nasopharynx so that adenoid tissue is clearly shown in contrast with the air in the nasopharynx.

The interpretation of the roentgen films of the sinuses rarely offers any difficulty except in the very young infant in whom, because of the small size of the ethmoids and maxillaries, it is frequently difficult to recognize minor changes. The usual observation in adenoid bronch sinusitis is irregular thickening of the mucous membrane lining of the paranasal sinuses with or without retained secretions. Adenoid tissue is always excessive and produces a prominent soft tissue shadow



Fig 85—Lateral film of nasopharynx. The excessive adenoid tissue is outlined by arrows.

on the posterior nasopharyngeal wall (Fig 85). Frequently this collection of lymphoid tissue is so abundant that the nasopharyngeal airway is all but occluded. The faucial tonsils are not recognizable on the lateral film. The chest films will in all cases show slight prominence of the hilar shadows and considerable accentuation of the bronchovascular markings. In the older children the prominent markings are most evident at each lung base, while in the young infant because of the habitual prone or supine position the most prominent changes will be in the right upper lobe. Some perivascular congestion is often observed and occasionally indefinite areas of peribronchial thickening or infiltration may be seen. Aeration of the lungs is usually somewhat

irregular with slight peripheral emphysema or localized bulging of one or more of the rib interspaces and occasional areas of lobular diminution in volume. These latter changes are more easily recognized and more frequently observed in the infant chest.

In summation, one may say that the roentgen examination reveals evidence of sinusitis, excessive adenoid tissue and reactive changes in the chest due to chronic postnasal "drip" and bronchitis with a frequently associated peribronchial pneumonitis.

#### TREATMENT

The success of the treatment of this condition depends on our ability to separate from the large group of patients suffering from bronchitis and sinusitis those patients in whom the primary cause of the disease is infection and hypertrophy of the adenoid tissue.

**Sulfadiazine**—With the diagnosis of adenoid bronchosinusitis established, our patients are given a 3-day course of sulfadiazine, usually in their own homes. The dosage of sulfadiazine used is from  $\frac{3}{4}$  to 1 grain (0.05 to 0.065 gm.) per pound of body weight, accompanied by an equal number of grains of sodium bicarbonate. The total 24-hour dosage is given in from three to five installments. With infants and small children the tablets are crushed and administered mixed with one or two teaspoonfuls of cereal, prune pulp or applesauce. The parent is instructed to give fluids during this period to a total of from 2 to 3 ounces per pound of body weight per 24 hours. The parent is also warned to watch for signs of a skin eruption and for scanty or bloody urine.

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After completing this preliminary course of therapy, the child's adenoids or tonsils and adenoids are removed.

**Adenoidectomy and Tonsillectomy**—The operation is performed after premedication with fairly large doses of nembutal given preferably one hour before operation is scheduled. Gas-oxygen induction followed by ether anesthesia is used and the table is kept tipped in the Trendelenburg position throughout the operation. The adenoids are removed with Barnhill curets and the nasopharynx is temporarily packed with sponges to which strings are attached. The tonsils are removed by sharp and blunt dissection with knife and right-angle scissors and a snare is applied to the base of the tonsillar pedicle. As much of the lymphoid tissue in the plica triangularis as possible is removed by dissection down to the dorsum of the tongue. If bleeders are encountered, they are controlled with No. 000 plain catgut sutures. The tonsillar fossae and adenoid bed are then insufflated with sulfadiazine powder.

After the operation the patient returns to bed and is kept with his head on the side and a sandbag or folded sheet under his chest. Postoperatively he is kept under fairly large doses of codeine given hypodermically. There is normally very little, if any, fever or reaction

The patient returns to bed perfectly dry. Postoperative bleeding has never been a problem in these cases. Postoperative packing or suturing has not been necessary in any of these patients. The patient usually stays in the hospital for 48 hours, and is then discharged home on sulfadiazine medication for 2 or 3 more days. The mother is instructed to watch the urine carefully for oliguria or hematuria, in which case the drug is discontinued. The fluid intake is kept as high as possible. The patient usually remains in bed for 4 days at home and then is up and about the house for another 3 or 4 days. During this time he is on a soft-solid diet with as much fluid as possible.



Fig 86—Lateral film of the nasopharynx made two weeks after adenoidectomy. There is no visible adenoid tissue.

**Shall the Tonsils Be Removed in Addition to the Adenoids?**—The decision as to whether the operation shall be limited to removal of the adenoid tissue or whether the tonsils should also be removed must be made from a study of each individual patient. If the tonsils are chronically infected and if there has been or is present, cervical adenitis in the tonsillar drainage area, the tonsils should be removed. In actual practice the lymphoid infection is so extensive that the tonsils have already been removed.

**Results**—The results of treating adenoid bronch sinusitis at the onset of the disease through a combination of chemotherapy and surgery have been most gratifying. The immediate results are often

dramatic, nasal breathing is established, nasal discharge disappears, night cough disappears and the child's general condition improves rapidly. Two boys put on 6 pounds each in 1 month, another gained 8 pounds in 3 months. The parents frequently comment on the return of "pep" and the disappearance of fatigue and irritability. Following this treatment the children may acquire respiratory infections but instead of the previous prolonged course they recover perfectly within a few days.

#### CONCLUSIONS

From the large group of children suffering from chronic infection of the sinuses and bronchi it is possible to separate a group in which the primary etiology is infection and hypertrophy of the adenoid tissue. The diagnosis of this group with adenoid bronchosinusitis is made by x-ray demonstration of excessive adenoid tissue obstructing the postnasal space. The surgical removal of this hypertrophied adenoid tissue is accomplished during the course of the disease through the help of chemotherapy. The results have been immediate and most gratifying.

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# ACUTE BRONCHIOLITIS IN INFANTS

EDWARD L. PRATT, M D \*

THE use of the sulfonamides, proper supportive measures, and good nursing care have greatly reduced the number of deaths from the common forms of bronchopneumonia in infants and children. Nevertheless, the usual methods of treatment may not prevent death in one form of primary bronchopneumonia, which has been called acute bronchiolitis. The treacherousness of this condition and the need for prompt, specially modified treatment make it worth while to consider acute bronchiolitis separately from the other types of bronchopneumonia.

Acute bronchiolitis occurs most frequently in infants 3 to 18 months of age. It is a syndrome characterized by rapid, labored respirations, audible wheezing, prostration, cyanosis, pulmonary emphysema, and signs of exudate in the smaller air passages leading to obstructive dyspnea and asphyxiation terminally. The terms bronchitis, capillary bronchitis, asthmatic bronchitis, or simply bronchopneumonia have been applied to this syndrome in the past. Bronchiolitis is more descriptive since it is this portion of the respiratory tract which is primarily involved, and the term has fewer ambiguous connotations than the others commonly used.

## CLINICAL FEATURES

**Early Symptoms**—Acute bronchiolitis generally appears as a primary disease. Usually there is a history of recent exposure to someone with an acute respiratory infection, which is often of a minor nature, such as a common cold or "grippe." The first evidence of illness in the infant are such symptoms as unusual irritability, refusal of feedings, and restless sleep. Slight cough and nasal discharge are the earliest indications of involvement of the respiratory tract. From the onset the cough is loose, and is often described as "deep down in the baby's chest." The respiratory rate is soon increased. The next serious symptom noted by the parents is noisy breathing, which is described as either "wheezing" or a "rattle in the chest." Diarrhea, or later vomiting, or both occur in almost half the patients. Early in the course of the disease elevation of temperature is not a prominent feature. Usually after 1 to 7 days of mild but progressive symptoms there is a rapid change for the worse in the infant's condition.

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From the Department of Pediatrics, Harvard Medical School, and the Infants' and Children's Hospitals.

\* Assistant in Pediatrics, Harvard Medical School, Junior Attending Physician, Infants' Hospital, Junior Attending Physician, Children's Hospital.

**Advanced Symptoms.**—The cough becomes more frequent and distressing, and the breathing extremely labored due to inability to get sufficient air into or out of the lungs. Often wheezing is audible. The child appears greatly distressed and seriously ill. Most often the duration from the first symptoms to pronounced illness is 2 to 7 days, but occasionally this course is of less than 24 hours duration, rarely the symptoms progress slowly and irregularly over 10 to 20 days.

The family history is noncontributory. Allergy or chronic infections of the respiratory tract are not more frequent in families of these patients.

The past history generally reveals that patients with acute bronchiolitis have had no predisposing illness. They have not had an unusual number of infections of the respiratory tract. Mild attacks of wheezing have occurred in about one third of the subjects.

**Physical Examination.**—The ordinary methods of complete physical examination yield sufficient information for the positive diagnosis of acute bronchiolitis when present in infants.

When a physician is first called, the *temperature* is most often from 102° to 103° F, but it may be normal or over 105° F. The pulse rate is usually rapid. The respiratory rate is generally between 60 and 80 per minute. In some cases the rate is only moderately elevated. Extremely rapid respirations may be seen in rare instances.

The development and nutritional state of these infants is good, upholding the past history of good health. About one-third of the infants are obese. Nearly one-half the infants are severely ill when a physician is first called. However, one must bear in mind that some of the cases which appear quite mild when first seen, will progress rapidly to alarming severity. The *responsiveness of the patient* is a valuable index of the gravity of the illness. The most seriously ill patients are apathetic and make no resistance to examination. Slight to moderate cyanosis is seen in about one-half of the cases.

One of the distinctive features of this syndrome is the *character of the respirations*. In addition to rapid and extremely labored breathing retractions of the soft tissues in the supraclavicular, subcostal and intercostal spaces are present. The accessory muscles of respiration are used, and the thoracic cage is fixed in the position of inspiration. Wheezing is frequently audible with each expiration. Since the character of the respirations is that of obstructive dyspnea, it is important to ascertain whether or not the larynx is involved. Patients with acute bronchiolitis alone have a prolonged expiratory phase and do not have the stridor nor the hoarseness indicative of laryngeal involvement. However, some patients with laryngitis or laryngotracheobronchitis retain chiefly from obstruction in the upper air passages, while retaining an adequate airway above. In these cases the pathologic obstruction, the disturbances in the lungs on physical examination, and the treatment are similar to those encountered in uncomplicated acute

bronchiolitis. Doubt as to the presence of, or the degree of, laryngeal involvement should lead one to have a consultation with a laryngologist in order to select correctly and early those patients in whom a tracheotomy, or some other surgical procedure, should be done.

Inspection of the *nose*, *throat* and *ears* reveals signs of inflammation in practically all cases, although suppurative otitis media is infrequent.

Percussion and auscultation of the chest bring out several distinctive features in patients with acute bronchiolitis. *Hyperresonance* is uniformly present. It is most marked in the lower two thirds of the chest anteriorly and laterally, with less resonance at the apices and in the paravertebral areas posteriorly. In but few instances can any convincing evidence of localized dullness be found, even though patches of atelectasis or consolidation may be present. Unless one is familiar with the normal resonance of the chest in infants at various ages and with various body builds, minor degrees of hyperresonance may be overlooked. Evaluation of breath sounds is apt to be difficult due to adventitious bronchial and tracheal noises and because of the diminished air exchange. Generally the breath sounds during inspiration are diminished in intensity and duration, with normal or slightly increased pitch, but true bronchial breathing is uncommon. The breath sounds during expiration are moderately prolonged and are increased in intensity and pitch, with respect to the inspiratory sounds. A *wheezing character* to the breath sounds is present in over one-half the cases. The most distinctive feature on auscultation is the presence of many *rales throughout both lung fields*. Almost always fine dry rales are heard, and, when numerous, are accompanied by expiratory, high pitched musical rales. In some instances the fine dry rales are obscured by coarse moist rales, sonorous musical rales, and bubbling sounds over the larger bronchi and the trachea. In general, the rales are less coarse and less intense than those in the usual case of bronchial asthma, but sometimes the adventitious sounds in acute bronchiolitis closely simulate those heard in asthma. True asthma is much less frequent in this age group than is bronchiolitis. Localized areas in which rales and alteration of breath sounds are concentrated are frequently observed, but such areas tend to be transient.

Examination of the *heart* reveals a rapid rate and apparent diminution of cardiac dullness with decreased intensity of the heart sounds. The latter two apparent abnormalities are due to the emphysematous lung tissue overlying the heart. In the severely ill patients, faint heart sounds of poor quality, with or without a gallop rhythm, may be present due to the effects of the infection and anoxemia on the cardiovascular system.

In many instances no abnormalities are noted in the abdomen although the edge of the liver or the tip of the spleen is sometimes felt. The organs may be displaced downwards by the pulmonary emphysema, or, in rare instances, may be enlarged due to passive con-

gestion secondary to circulatory failure. Occasionally abdominal distention is present. The abdomen is then tympanitic, but without tenderness or spasm, and peristaltic sounds are diminished or absent. In such cases the condition is generally due to adynamic ileus.

The skin is warm, of good turgor, and free of any eruption, unless circulatory collapse is present. Then the skin is cold, moist and mottled, with sluggish vasomotor responses.

The rest of the physical examination is usually within normal limits, thereby assuring one that the respiratory infection is the primary disturbance.

**Laboratory Data**—The white blood count is not uniformly altered. A moderate leukocytosis is present in about one-half the patients. A leukocyte count of less than 6000 per cubic millimeter is present in a few instances, a normal count in about one third of the cases. The remainder of the blood studies and the urine examination reveals no significant changes. Cultures from the nasopharynx and throat produce the usual pathogens in no characteristic pattern. Beta hemolytic streptococci, pneumococci, *Staphylococcus aureus* and *Haemophilus influenzae* are usually present in various combinations. Occasionally only one of these organisms is isolated, and in rare cases no bacterial pathogens are detected. Blood cultures are almost always sterile.

**Roentgenologic Examination**—Roentgenograms of the lungs reveal certain characteristic changes.<sup>1</sup> The most uniform alteration is emphysema involving all portions of the lungs. Bulging of the emphysematous lung tissue into the interspaces is a prominent feature. There is an increase in the bronchovascular markings and varying degrees of peribronchial infiltration. Small patches of pneumonic consolidation or atelectasis may be seen close to the hilum and towards the bases. Close inspection of the films reveals irregularity of aeration with multiple small areas of emphysema, surrounded by normal or partially atelectatic lung tissue. Such irregular aeration is due to varying degrees of bronchial and bronchiolar plugging. The mediastinum is not displaced. Fluoroscopic examination is apt to be deceptive since the lung fields appear unusually bright and no large areas of increased density are seen. However, the observations that the diaphragm is depressed and moves very little, and that the thoracic cage appears to be fixed in the position of extreme inspiration will aid in a correct interpretation.

**Course**—The course in untreated or improperly treated cases is marked by steadily increasing obstructive dyspnea which, coupled with the progressive anoxemia, may lead to exhaustion and death. Even in properly treated patients the course is variable. In spite of all measures, some of the infants die within the first few days, especially if accompanied with rapidly progressing symptoms and those nearly moribund when first seen. The majority of the patients have a slight increase in the signs of toxemia for a day or two but proper treatment results in

a lessening of their respiratory distress within a few hours. Their temperatures reach normal in 3 to 7 days and they appear well in a few more days. A few medium to coarse rales may persist for an additional week or more. A small proportion of the infants, although seriously ill, make a rapid recovery within a day or two. Only rarely does acute bronchiolitis progress into a protracted bronchopneumonia. Such an occurrence should lead one to suspect the presence of some other disease or some underlying disturbance, such as pancreatic fibrosis or the aspiration of foreign substances.

### PATHOLOGIC CHANGES

Brief comment on the pathologic changes is useful for the understanding of the clinical signs and especially for the planning of treatment.

The basic pathologic process is inflammation of the entire thickness of the walls of the bronchioles, resulting in a spread of the inflammatory reaction to the interstitial tissues around the bronchioles, blood vessels and lymphatics, and into the walls of adjacent alveoli. This process leads to a progressive lymphangitis and to involvement of the alveolar spaces. Such changes are essentially those described by McNeil, MacGregor and Alexander<sup>2</sup> in cases of bronchopneumonia.

**Gross Examination**—On gross examination the lungs are voluminous with considerable emphysema in the anterior and upper portions. They are two to three times their normal weight. Edema and congestion account for most of this increased weight. The lungs have numerous blotchy purplish areas with increased firmness. The cut surface reveals purulent material in the bronchi and bronchioles which have thickened walls and protrude from the general surface. In most cases small areas of consolidation are seen surrounding the bronchioles. Generally the pleural surfaces are smooth with dilated subpleural lymphatics. The lymph nodes around the trachea and bronchi are swollen to three to four times their usual size. Generally, there are no additional outstanding gross findings in other organs, except for toxic reaction in lymphatic structures and considerable increase in the weight of the brain, which is congested and edematous.

**Microscopic Changes**—Microscopic examination of sections from the lungs of patients with acute bronchiolitis shows the bronchiolar lumens to be filled with mucus and necrotic debris. The entire wall of the bronchioles is infiltrated with polymorphonuclear and especially mononuclear cells. A similar infiltration is present around the blood vessels and lymphatics. There is congestion, edema and infiltration of the alveolar walls. The alveolar spaces are generally clear except close to the affected bronchioles. In these areas the alveolar spaces contain an inflammatory exudate. In some cases the alveolar spaces throughout the lungs contain edema fluid or hemorrhagic exudate. Sections of the heart muscle may show edema and increased

numbers of fat droplets. Microscopic examination of the central nervous system usually discloses only vascular congestion, and edema of the cells and extracellular spaces.

### CAUSATION

The syndrome of acute bronchiolitis is probably produced by any agent capable of causing an acute inflammatory reaction in the bronchioles, rather than by any specific virus or bacterium. Hubble and Osborne<sup>3</sup> considered acute bronchiolitis to be related to infections with the virus of influenza. We at the Infants' Hospital, as well as Greengard, Raycraft and Frank,<sup>4</sup> have noted the occurrence of epidemics of bronchiolitis, which is suggestive of a specific causative agent.

### TREATMENT

The treatment of patients with acute bronchiolitis consists of attacking the infection, the respiratory distress, the oxygen lack and the circulatory collapse.

**Infection**—Since there are probably a variety of causative agents producing the infection, no single therapeutic measure gives uniform results. However, bacterial infection plays an important role in many cases. Hence, the use of an appropriate sulfonamide is justified for those patients with a rapid progression of symptoms, and especially those appearing critically ill.

**Sulfadiazine**—Sulfadiazine is the drug we have most frequently employed. It is effective against most of the commonly encountered pathogens, has relatively few toxic manifestations, and is easily administered. A period of observation before giving sulfadiazine is proper in the milder cases.

If one decides to use sulfadiazine it should be given in proper dosage to secure concentrations in the blood of from 8 to 15 mg per 100 cc. No therapeutic effect can be expected from doses which are either too small or too infrequent. Most of the patients with acute bronchiolitis are fairly well hydrated, have no impairment of renal function, and can be given an adequate fluid intake. Therefore, full doses of sulfadiazine may be used from the start. If administered orally to infants under two years of age, an initial dose of 0.1 gm per kilogram of body weight ( $\frac{2}{5}$  grain per pound) followed by 0.2 gm per kilogram per day ( $\frac{1}{2}$  grain per pound per day) divided into three, four or six doses has been found to give satisfactory sulfadiazine concentrations in the majority of instances.

Subcutaneous injections of a 5 per cent solution of sodium sulfadiazine as recommended by Jorgensen and Greeley<sup>5</sup> have been used over a year at the Infants and Children's Hospital without untoward reactions. This method of administration is particularly useful in critically ill infants who may vomit medications given by mouth.

When injected subcutaneously a smaller amount of the drug is necessary to obtain adequate blood levels than when administered by mouth. When the subcutaneous route is used, the initial dose should be 0.06 to 0.08 gm per kilogram of body weight ( $\frac{1}{2}$  to  $\frac{2}{3}$  grain per pound), to be followed in 8 hours by 0.04 gm per kilogram of body weight ( $\frac{1}{3}$  grain per pound) every 8 hours until the drug can be retained by mouth. The above dosages are merely tentative and must be altered according to the concentrations of sulfadiazine in the blood which should be determined in order to insure that the critically ill patient is receiving adequate therapy.

Many physicians advise the use of *alkalies*, such as sodium bicarbonate, sodium citrate or sodium lactate, in doses of 0.03 gm per kilogram of body weight ( $\frac{1}{4}$  grain per pound) every 4 hours in conjunction with sulfadiazine. We have found that if an adequate output of urine is maintained, infants rarely have renal complications from sulfadiazine, even when no alkali is given.

*Transfusions Parenteral Fluids*—Blood or plasma transfusions are of use, both to maintain the oxygen carrying capacity and the osmotic properties of the blood, and to provide nonspecific antibodies. During the acute phases of the illness 5 per cent dextrose or equal parts of 10 per cent dextrose and physiological saline by mouth are better tolerated than milk or other foods. Excessive or too rapid administration of parenteral fluids to patients with acute bronchiolitis may cause greater respiratory distress. Generally, adequate amounts of fluids, 120 to 170 cc per kilogram of body weight per day, can be given by mouth supplemented daily with one or two hypodermoclyses consisting of equal parts of 5 per cent dextrose in water and physiological saline. If metabolic acidosis is known to be present, one-sixth molar sodium lactate solution may be substituted for the saline in the hypodermoclyses. Intravenous fluids may be necessary, but should be given cautiously. Excessive administration of sodium ions, parenterally or orally, is to be avoided.

*Respiratory Obstruction*—The respiratory distress is due largely to the obstruction of the bronchioles. The resulting emphysema diminishes the vital capacity to the dyspneic point. Both these factors diminish air exchange and alveolar ventilation, thus beginning the chain of events which results in stimulation of the respiratory center to produce hyperpnea. The violent respiratory efforts, the obstruction, and the anoxemia all promote the escape of fluid from pulmonary capillaries into the interstitial tissues of the bronchiolar mucosa, into the alveolar stroma, and eventually into the alveolar spaces. Hence, to relieve the respiratory distress one must combat primarily the obstruction of the finer air passages. Air with a relative humidity of 95 to 100 per cent has proved to be the most useful single agent in relieving the respiratory obstruction. The cool moist air aids in liquefy-

ing the bronchiolar secretions and preventing crust formation. In addition, excessive insensible fluid loss from the lungs and skin is diminished. Croup tents, steam inhalations and other methods employing moist warm air are of some aid, but have numerous disadvantages. The provision of air at room temperature with a relative humidity of 95 per cent or more may be accomplished by the use of *mechanical humidifiers*, such as described by Davison.<sup>6</sup> Small closed rooms with one to three humidifiers\* in operation have been used for a number of years at the Children's Hospital and have been found to be more satisfactory, both for the patients and for those attending them, than other methods tried.

Spasm of the bronchi and bronchioles is often present, and is occasionally relieved by doses of *epinephrine*, 0.12 to 0.18 cc (2 to 3 minims) subcutaneously, every 30 to 60 minutes. *Theophylline ethylenediamine* (aminophylline) usually given in combination with 50 per cent dextrose intravenously has been found to be more effective in most cases. In many instances the response to this mixture has been most dramatic, whereas in a few no benefit is noted, and in rare cases the obstructive dyspnea has been made worse, probably due to drying of the secretions. Theophylline ethylenediamine combined with 50 per cent dextrose not only relieves spasm of the bronchioles but also aids by reducing the edema of the respiratory mucosa, of the alveolar spaces and interstitial tissue, and of the brain. Satisfactory therapeutic effects with theophylline ethylenediamine, without untoward reactions, have been achieved with doses of 0.006 gm per kilogram of body weight ( $\frac{1}{2}$  grain per pound) combined with 2 cc per kilogram of body weight (1 cc per pound) of 50 per cent dextrose given slowly intravenously. This mixture may be repeated every 6 to 8 hours if effective, but should be discontinued if there is any tendency towards thickening of the secretions. *Expectorants* given by mouth are of little value, due to the small margin between the expectorant and emetic doses for ill infants, probably already nauseated and with a tendency towards vomiting. Great care should be exercised in the use of *sedatives*. Restlessness due to respiratory obstruction should be treated by relieving the obstruction and not by sedatives. Since practically maximal respiratory efforts are necessary in order to provide sufficient pulmonary ventilation to sustain life, opium derivatives or other respiratory depressants are to be avoided. Except in carefully selected cases, *atropine*, by thickening the secretions in the bronchioles and bronchi tends to be harmful.

**Oxygen Lack.**—In nearly all cases, except the mildest there is diminished oxygenation of the blood. Visible cyanosis is frequently seen. The importance of oxygen lack is often not appreciated until irreversible physiologic changes have taken place. Anoxemia contributes

\*Walton Humidifier, Model N., Walton Laboratories, Irvington, N. J.



to the escape of fluid from capillaries, especially in the lungs and central nervous system. Hence, oxygen therapy should be instituted early and freely. However, oxygen tends to thicken the bronchiolar secretions. It should, therefore, be used in combination with moist air. Only rarely is sufficient moisture for treating patients with bronchiolitis obtained by merely bubbling the oxygen through a water bottle. The administration of oxygen by means of a *nasal catheter* is efficient and economical, but difficult to keep in place in restless infants. Small open-topped *oxygen tents* in a room filled with moist cool air are highly satisfactory. Unless one is certain from previous experiences that the equipment employed reliably provides the desired concentrations, one must measure the oxygen concentration of the inspired air.

**Circulatory Collapse**—The dearth of effective measures makes it difficult to treat circulatory collapse. The type of shock or collapse resulting from severe infections, so-called "medical shock," was shown by Ebert and Stead<sup>7</sup> to respond only after elimination of the infection. Hence, the prompt and proper use of sulfonamides, blood or plasma, oxygen, and measures to relieve the respiratory distress must be relied upon to prevent "medical shock" and to treat it. Caffeine with sodium benzoate 0.03 to 0.13 gm ( $\frac{1}{2}$  to 2 grains) or metrazol 0.25 to 0.5 cc (4 to 8 minims) may be used in the treatment of respiratory depression.

**Nursing Care**—Much is accomplished by proper nursing care in order to maintain the proposed therapy and to provide the maximum of comfort and rest for these patients. *Abdominal distention* is treated by enemas, rectal tubes, heat to the abdomen and, in certain cases, by pitressin 0.5 to 1.5 units intramuscularly or prostigmine methylsulfate 0.25 to 1 cc (4 to 16 minims) of a 1:4000 solution intramuscularly or subcutaneously.

#### SUMMARY

Acute bronchiolitis is an infection of the lower respiratory tract, characterized by the following symptoms and signs:

- 1 Slight malaise and mild irritability progressing more and more rapidly to marked restlessness and great distress, followed by apathy and grave illness.
- 2 Cough and rapid respirations becoming more labored, with inspiratory retractions and prolonged, wheezing expirations.
- 3 Evidence of inflammation of the nose, throat, and ears without significant involvement of the larynx.
- 4 Hyperresonant lung fields in which the breath sounds are diminished. Fine dry rales and varying numbers of musical rales widely distributed, although sometimes partially obscured by coarser moist and musical rales.

The methods useful in combating some of the disturbances encountered in cases of acute bronchiolitis may be outlined as follows,

- 1 *Infection* Sulfonamides in adequate doses, possibly supplemented by blood or plasma transfusions.
  - (a) Sulfadiazine 0.2 gm. per kilogram of body weight per day if administered orally, or 0.04 gm. per kilogram of body weight every eight hours if injected subcutaneously as a 5 per cent solution of sodium sulfadiazine.
- 2 *Bronchiolar Obstruction*. Cool moist air with a relative humidity of 95 to 100 per cent.
- 3 *Bronchiolar Spasm and Edema of Lungs and Brain* Theophylline ethylenediamine (aminophylline) 0.006 gm. per kilogram of body weight combined with 50 per cent dextrose 2 cc. per kilogram of body weight given slowly intravenously every 6 or 8 hours if effective.
- 4 *Anoxemia* Early and free use of oxygen, in combination with moist air, by means of a small open-topped oxygen tent or nasal catheter.
- 5 *Symptomatic Treatment*
  - (a) Adequate nursing care
  - (b) Reduced diet, or only clear fluids by mouth
  - (c) Fluid intake, by all routes, of about 120 to 170 cc. per kilogram of body weight
  - (d) Control of abdominal distention
  - (e) Avoidance of respiratory depression. Caution in the use of intravenous fluids, and prevention of excessive intake of sodium ions.

### CONCLUSIONS

Acute bronchiolitis in infants has been discussed with reference to the clinical features, the major pathologic changes, and probable etiology. A detailed plan of treatment for the various disturbances frequently encountered has been presented.

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# TREATMENT OF COMMON EAR, NOSE AND THROAT PROBLEMS BY THE GENERAL PRACTITIONER

## Therapeutic Rationale

FRANCIS L. WEILLE, M D \*

THE purpose of this paper is to supply useful information for the general practitioner in the treatment of some of the commoner ear, nose and throat conditions. It is not meant to be complete, for more detailed information a treatise such as Lederer's<sup>1</sup> should be studied.

### FUNDAMENTALS

Three fundamentals must be recognized by the general practitioner for reasonable success in treatment. (1) There is nothing mysterious about the diseases of the ears, nose and throat. The same general principles apply here as in diseases of any other part of the body. If the lesion causing the patient's complaints can be recognized by the general practitioner, and if he is familiar with the more general details of the anatomical and physiological relations of the structure involved, an ordinary knowledge of pathology and practical therapeutics will enable him to give the patient satisfaction in the majority of cases. (2) An adequate *case history* is necessary. (3) A *physical examination* (with appropriate laboratory work) in relation to the ears, nose and throat should be done in every otolaryngological case, as in any medical problem.

**History**—The history should include inquiries regarding

1 *Nasal obstruction*. Patients with atrophic rhinitis never complain of nasal obstruction. The presence of obstruction suggests acute or chronic rhinitis, nasal polyps, foreign body, gross deviation of the septum, or vasomotor rhinitis.

2 *Nasal discharge*. Yellow and mucopurulent discharge suggests the presence of sinusitis. Thin, watery discharge indicates acute rhinitis, vasomotor rhinitis or hay fever. Expulsion of thick crusts which are foul smelling to others but not to the patient may mean atrophic rhinitis. Persistent unilateral slight or moderate blood-tinged nasal discharge in an elderly person, if associated with obstruction of that side, is a usual history in sinus malignancy.

3 *Sneezing* points toward hay fever, vasomotor rhinitis, or early acute upper respiratory infection.

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From the Department of Otolaryngology, Harvard Medical School, and the Otolaryngological Service of the Massachusetts Eye and Ear Infirmary.

\* Assistant in Laryngology, Harvard Medical School, Associate Surgeon, Massachusetts Eye and Ear Infirmary and Massachusetts General Hospital.

4 *Postnasal drip* is evaluated in terms of the same conditions as nasal discharge in (2)

5 *Headache* Proetz<sup>2</sup> has emphasized that there are about thirty causes for headache. Nasal headache is usually either from sinusitis or pressure between the medial and lateral nasal walls. Headache complicating ear sepsis is usually a serious symptom, often pointing toward a complication of middle ear or mastoid infection.

6 *Sore throat* Every practitioner is familiar with numerous varieties of sore throat. It should be emphasized that tender glands in the neck often result in the complaint of a "sore throat" for many weeks.

7 *Hoarseness* for a short period of time suggests acute laryngitis, intermittent hoarseness, chronic laryngitis, chronic hoarseness may possibly mean carcinoma, tuberculosis, lues, polyp or papilloma of the larynx.

8 *Chronic difficulty in swallowing* solids or soft solids demands fluoroscopy of the hypopharynx and esophagus. Difficulty with fluids but not solids points toward laryngeal pathology, such as cord paralysis.

The auricles, mastoids, external auditory canals and drums are examined. With a complaint of vertigo nystagmus should be looked for, a Romberg test done and the gait observed. The hearing of each ear is tested conveniently by using low whisper and conversation which are normally heard at 20 feet. The ear not being tested is corked with the patient's forefinger, his eyes are closed. Deafness for a watch tick is indicative of *high* tone hearing loss ("nerve" deafness) beyond the conversational range of about 300 to 3000 cycles. *Low* tone loss ("middle-ear" deafness) is most easily determined with tuning forks (specialists also use the audiometer).<sup>3</sup>

### APPLIED PHYSIOLOGY OF THE NOSE

For rational nasal therapy it is of great help to nonspecialists to understand some of the principles of nasal physiology. The nose is fundamentally an air-conditioning organ. It warms the respired air from the temperature of the environment to about 90° to 94° F. in its passage through the nasal cavities to reach the nasopharynx. About 25 per cent of body heat is utilized for this purpose.<sup>4</sup>

The nose secretes almost as much fluid in 24 hours as the kidneys. It is estimated that it produces each day about a liter of fluid, of which about 70 per cent is used for humidifying respired air and 30 per cent for the preservation of a mucous blanket over the ciliated epithelial surface. When the air passes through the nose from the nasal vestibule to the nasopharynx, it becomes about 80 per cent humidified.<sup>4</sup> By the time it reaches the trachea the relative humidity is about 95 per cent.

The *mucous blanket* is important in understanding the methods of treatment of the nose. This is a *watery* film of mucinous material which extends from just posterior to the nasal vestibules to the stomach. In the nose it is propelled posteriorly by the action of the cilia. An analogy is an ordinary escalator stairway where the moving platform upon which one stands is equivalent to the mucous blanket, while the mechanism which propels the platform corresponds to the cilia of the pseudostratified ciliated columnar epithelium. In the anterior portion of the nasal cavities, from the nasal vestibules to the region of the anterior tips of the middle and inferior turbinates, there are no cilia, and therefore the mucous blanket moves more slowly here. The film is dragged from before backward over the nonciliated cells by ciliary streaming posteriorly.

The same ciliary streaming occurs normally in all sinuses, with the direction of streaming in general toward the sinus ostia, although not necessarily directly. Inflammatory changes in sinuses, including purulent exudate on the surface of a sinus, will not stop ciliary streaming. Therefore, in any form of sinusitis, *if the sinus ostia are kept open, it is possible for pus in an accessory air cavity to drain*. The sinus ostia are the "bottle necks" where swelling of the mucosa may mechanically obstruct drainage. A deviated septum may cause no mechanical difficulty in the *absence* of nasal or sinus infection but may be important when the swelling of infection occurs.

Any drying of the mucous blanket will stop ciliary activity, so may poorly selected nasal medications such as 1:1000 adrenalin used for shrinkage of the mucosa.

Normal ciliary streaming acts as a self-cleaning mechanism for the nose and sinuses. Thus, the nasal cavities are normally sterile, or almost so, in their middle thirds at least, because of the rapid removal of any bacteria which may fall upon the mucous blanket. Such bacteria remain in the anterior portion of each nasal chamber much longer because of the absence of cilia.

When a culture is taken from the nose, the sterile swab should not be allowed to be contaminated by the heavily infected nasal vestibules. Obviously infected material, such as pus from the middle meatus, should be utilized for examination. In the absence of pus, material from the region of the anterior tip of the middle or inferior turbinate offers the best chance for obtaining a satisfactory specimen.

The physiology of the mouth, pharynx and larynx is familiar to most practitioners. Even though the salivary glands normally secrete about 1500 cc. of saliva daily, the mouth is inadequate for air-conditioning of respired air and a dry throat will be complained of usually after about an hour of complete nasal obstruction.

### THE HEAD COLD

The head cold is the commonest of all diseases. It is remarkable that physicians accept with equanimity the axiom "There is no treatment for a common cold. Treated, it lasts ten to fourteen days, and untreated the same length of time."

Linsner<sup>5</sup> accepted this position, but in his visits to the writer for treatment of his occasional colds "for comfort" he flatly stated that *cold virus infection is self-limited and lasts only 12 to 72 hours*. It is probable that *secondary infection with ordinary pathogenic bacteria causes both the persistence and complications of head colds*. If such secondary infection can be avoided, the illness will be shortened, and the patient will think that he is "cured."

An attempt to avoid this secondary infection has been reported by Pickrell and his associates,<sup>6</sup> who used 2.5 per cent sulfadiazine in 8 per cent triethanolamine in distilled water as a nose and throat spray. It was employed eight to twelve times a day for the first 3 days, and five to eight times daily for the second 3 days. Pickrell<sup>7</sup> had previously shown that a large burned area on the skin could be kept far more sterile by spraying it frequently with this solution than by giving sulfadiazine by mouth. He infers<sup>8</sup> that the solution does not affect ciliary action, and that its hydrogen ion concentration is suitable for spraying the tissues of the nose and throat. Crowe<sup>9</sup> recommended this preparation in 1942.

I have employed Pickrell's solution for approximately the past two years in the treatment of several hundred patients with common colds, and in those who appear with acute sinusitis already established. The effect has apparently been beneficial in many cases. The following prescription is recommended:

- ℞ Pickrell's solution 60 cc. (3ii)  
 Dispense DeVilbiss No. 251 atomizer \*  
 Sg Spray throat and both nostrils every 2 hours.

If it is desired to state the content of this prescription chemically it may be written

- ℞ 2.5% sulfadiazine in  
 8% triethanolamine in  
 distilled water

60 cc (3ii)

\* Available in most pharmacies.

In view of the facts mentioned in discussing the physiology of the nose, it is desirable to use a shrinking solution to lessen swelling of the nasal mucous membrane and to keep sinus ostia open, without impairing ciliary activity. The following is useful:

- ℞ Privine hydrochloride 0.1% aqueous solution 30 cc (℥i)  
 Dispense dropper in bottle  
 Sig 3 drops in each nostril every 2 hours  
 (This solution should be in 0.05% strength for children)

The nasal spray and the drops are used alternate hours, *not* together.

Because drying<sup>4</sup> of some point in the mucous blanket (usually near the anterior tip of the middle turbinate or in the nasopharynx) probably permits entrance of the cold virus at the onset of the common cold, nasal inhalations of unmedicated steam at 2-hour intervals for 5 to 10 minutes at a time are recommended, together with reasonable humidification of the environment to 30 to 45 per cent. The latter is accomplished by having a teakettle boil in the room for a few minutes of each hour, the former by the use of a thick-walled crockery pitcher containing steaming water, with an inverted paper bag making a lid for the pitcher. The steam is sniffed from a hole torn near the bottom of the paper bag.

Other shrinking medications may be employed instead of the privine hydrochloride. The following preparation is useful:

- ℞ Neosynephrin hydrochloride 0.25% aqueous solution 30 cc (℥i)  
 Dispense dropper in bottle  
 Dispense DeVilbiss No. 251 atomizer  
 Sig Spray both nostrils every 2 hours

The strength of the solution may be made greater—up to 1 per cent—if the nasal mucous membrane is found to shrink poorly. Other modifications include the addition of sodium chloride, 0.24 gm (4 grains), or glucose, 0.24 gm (4 grains), or neosilvol, 0.4 gm (6 grains). Ephedrine hydrochloride may be substituted for neosynephrin in the above prescription in a strength of 1, 2 or 3 per cent; the same modifications may be used. The bitter taste of an ephedrine salt may be easily disguised by saccharine, 0.016 gm ( $\frac{1}{4}$  grain) or 0.032 gm ( $\frac{1}{2}$  grain) to the ounce (30 cc) of solution. Alternative substitutions for neosynephrin are 1 per cent propadrine hydrochloride or 1 per cent paredrine hydrobromide. A benzedrine inhaler is sometimes found useful in shrinking the nasal mucosa.

*In patients having hypertension, adrenergic shrinking preparations must be avoided.* A substitute having no effect on the circulatory system but suitable for use in the nose is the following:

- ℞ Tuamine sulfate 1% aqueous solution 30 cc (℥i)  
 Dispense dropper in bottle  
 Dispense DeVilbiss No. 251 atomizer  
 Sig Spray both nostrils every 2 hours

It is difficult to persuade patients having the common cold to go to bed. They will usually agree to *sleep 10 or 12 hours of each day* and thereby secure as much rest as possible in spite of carrying on a minimum of activity. Other supportive measures include the avoidance of chilling, sleeping in a room which is not cold, forcing fluids and avoiding constipation. So far as possible there should be no contact (e.g., through the common washbowl used by families) with others who, themselves, have acute upper respiratory infections.

Errors in diagnosis regarding head colds are very frequent among those physicians who never make a physical examination of the nose or nasopharynx. Acute, subacute or chronic sinusitis, vasomotor rhinitis, even hay fever and atrophic rhinitis may all cause confusion since the patient calls his complaint a "cold." This fact makes some of the statistical studies of the common cold unreliable.

*Pale* nasal mucous membrane usually means allergic or vasomotor rhinitis, the red mucosa of the ordinary head cold can be differentiated from "red" vasomotor rhinitis by the fact that in the latter condition nasal smears often show a high percentage of eosinophils or eosinophilic plasma cells—just as in "pale" vasomotor rhinitis.

#### ACUTE SINUSITIS

*Sinus drainage is accomplished by ciliary streaming, not gravity.* Medical therapy designed for "dependent drainage" of the accessory air cavities of the nose disregards this fundamental physiological fact. The mucous blanket is propelled to the sinus ostium, regardless of the anatomical position of the ostium, whether "uphill" or otherwise. Furthermore, *ciliary streaming persists in the presence of infection*.<sup>4</sup>

There are therefore three fundamental purposes in rational treatment of acute sinusitis: (1) to keep the sinus ostia open, (2) never to damage the normal mechanism provided by nature for drainage, (3) supportive therapy.

The measures outlined elsewhere for the *prevention* of acute sinusitis as a complication of the common cold are employed if the patient presents himself with the acute sinus infection already established. However, after a few days the use of the sulfadiazine spray is gradually lessened, then omitted. The adrenergic shrinkage of the nasal mucosa is continued for 2 weeks, diminished to intervals of about every 3 hours the third week, and to about every 4 to 6 hours for an additional month.

During the most severe stage of the sinusitis, especially if there is much headache or sinus tenderness, the physician may use nasal tampons to shrink the mucous membrane in the region of the sinus ostia, especially in the middle meatus. One of the adrenergic drugs mentioned above—especially neosynephrin hydrochloride in 0.25 per cent aqueous solution—is soaked in very thin long fiber cotton tampons. While quite wet but not dripping, the tampons are placed in each



nostril for 2 or 3 minutes, then removed, so that with the added room obtained by shrinkage fresh tampons can be gently invaginated into the middle meatus. These are left *in situ* for half an hour or longer before removal, if easily tolerated. If pain is not then relieved, at the next treatment 0.5 per cent cocaine muriate is added to the shrinking solution, but the "packing" must be removed within a few minutes as cocaine is a potent and toxic remedy. The cocaine should be discontinued as soon as possible. The nasal tamponade may be employed daily until pain is controlled (or even twice daily if necessary), and occasionally thereafter. Any general practitioner who can use a head mirror with reflected light can manage this simple technic skillfully, since he has *two hands free* with which to work—one to hold a nasal speculum, the other the nasal forceps carrying the tampon. Such intranasal technic should never be attempted by "flashlight" illumination for fear of damaging the delicate mucosa.

If there is any appreciable temperature elevation, or if the patient seems "toxic," sulfonamide treatment by mouth should be started. Sulfadiazine is the drug of choice, and is given in a dosage of 0.65 gm (1 grain) per pound of body weight per day, divided into six doses. The 24-hour volume of urinary output must be measured and recorded, it must be above 1000 cc, or better, 1500 cc. The urine should be kept alkaline (as by giving sodium bicarbonate, citrocarbonate, etc.) The urinary hydrogen ion concentration can be determined instantly by using nitrazine paper dipped in a urine specimen and matched against a chart which accompanies such paper. The urine is checked every 2 days for the presence of red cells, sulfadiazine crystals are *normally* found in *cold* urine and may be disregarded. The patient's fluid intake is measured and recorded, it should be above 3000 cc per day. Blood counts (red count, white count, hemoglobin, and differential) are made every 2 days, as is a determination of the sulfadiazine blood level if possible. Nasal cultures, taken as described under nasal physiology, are planted both aerobically and anaerobically. Sulfonamide therapy is terminated after two days of normal temperature, and with rare exceptions always within one week.

If it is practical to do so, sinus x-rays are taken immediately whenever acute sinusitis is suspected. If the antrum is involved, films of the upper teeth are also included, since about 15 per cent of maxillary sinusitis is caused by abscessed tooth roots (molar or premolar). The x-rays offer the added advantage that comparative films may be taken 6 weeks or 2 months later to see if cure has resulted. If, at any stage of the illness, the course is not entirely favorable, a rhinologist must be consulted.

#### SORE THROAT

It is probable that general practitioners are thoroughly familiar with almost all details of the diagnosis and treatment of sore throat. The following suggestions are meant only to be supplementary.

**Diagnosis.**—1 It is always desirable to determine, by means of smears and aerobic and anaerobic cultures, the pathogenic organism in every throat in which there is definite exudate, particularly in every patient who has even a degree of temperature.

2 A routine blood examination to include a white count, differential, red count, and hemoglobin is equally desirable and *must be done in every case in which the symptoms do not subside within 48 hours*. Infectious mononucleosis, agranulocytosis, leukemia and similar conditions may thereby easily be ruled out.

3 A darkfield examination may be of little value because innocuous spirochetes normally found in the mouth secretions may be mistaken for the *Treponema pallidum*.

4 It should be remembered that Vincent's organisms may normally be recovered from recesses between the teeth.

5 The scarcity of diphtheria patients today tends to make the general practitioner forget that diphtheria still does occur and that an early diagnosis in such a case must be made.

6 Sometimes leukemia or a lymphosarcoma may be mistakenly diagnosed as a peritonsillar abscess. The noninflammatory character of the lesion helps in the differential diagnosis, a real quinsy itself is rarely mistaken.

7 Retropharyngeal abscess may be missed because of uniform displacement forward of the posterior oropharyngeal wall. In any case in which there is suspicion of such a lesion, a lateral x-ray film of the neck should be taken to determine the actual amount of retropharyngeal swelling present. It should be remembered that retropharyngeal abscess may extend from the base of the skull to the mediastinum.

8 Never fail to palpate the neck for tender cervical glands which may make a sore throat persist for weeks if untreated.

**Treatment.**—1 *Chemotherapy.*—The sulfonamide drugs given orally are recognized as the most valuable single therapeutic measure in severe infectious sore throats. When adequate quantities of penicillin are available it is likely that this statement will have to be revised.

2 *Irrigations.*—Sulfonamide treatment is supplemented by local measures including throat irrigations. These can be carried out by the patient at home. Normal saline is used: a level teaspoonful of salt is put into a quart of water which is boiled. When cool enough to pour on the finger it is ready for use. A douching apparatus, sterilized, is employed to irrigate the throat with the level of the salt solution container not more than a foot above the level of the mouth. The patient leans forward and holds his breath as he releases the solution into his throat from which it flows by gravity into a receptacle. The patient punches the tubing, breathes, holds his breath again and continues the irrigation.

3 *Heat.*—Hot flavseed poultices applied to the neck every 2 hours for 15 minutes give great comfort. Adequate precautions must be

taken to prevent a burn of the skin. The skin should be covered with petrolatum and the poultice allowed to cool adequately before application. A hot water bottle may be used in the intervals between poulticing.

4 *Gargles*—The gargle in the following prescription is antiseptic, analgesic, astringent, hypertonic, and is diluted with hot water.

℞ Phenol	4 cc (3i)
Zinc sulfate	8 gm (3ii)
Glycerin	60 cc (3ii)
Distilled water	q.s. ad 240 cc (5viii)

Mix and make a solution

Sig One-half teaspoonful in one-half glass of hot water for gargle every 2 hours

Another time-tried remedy is the following

℞ Phenol	0.7 cc (m℥)
Tannic acid	12.0 gm (5iii)
Glycerin	60.0 cc (3ii)
Distilled water	q.s. ad 240.0 cc (5viii)

Mix and make a solution

Sig One-half teaspoonful in one-half glass of hot water for gargle every 2 hours

5 *Sprays*—Pickrell's solution as a throat spray has already been discussed.

For soreness in the *nasopharynx* the following prescription is sometimes useful.

℞ Cocaine (alkaloid)	0.4 gm (gr vi)
Chloretone inhalant	ad 60.0 cc (3ii)

Mix and make a solution

Dispense DeVilbiss No. 251 atomizer

Sig Spray both nostrils every 2 hours

The precautions necessary in using oily sprays have been evaluated in a previous report.<sup>9</sup>

6 *Even severe Vincent's angina* will usually disappear in about a week or ten days if the lesions are swabbed once daily with Fowler's solution (liquor potassii arsenitis). This is done preferably by the physician. The patient is advised to use at home a peroxide mouth wash, "Vince" (sodium perborate), a level teaspoonful of powder in a glass of hot water, and S T 37 in a dilution of one to three with tap water (not hot). These medications are alternated every third hour, so that the treatment is hourly.

#### EPISTAXIS

A patient having a nosebleed of sufficient severity to call in a doctor usually is under the impression that he has lost a very large

amount of blood. The patient makes no distinction between blood diluted with saliva which is expectorated and whole blood dripping directly from the nose. He is, therefore, anxious and apprehensive when the physician arrives and is satisfied only with the complete arrest of the hemorrhage.

The nose is found full of blood clot, usually on both sides. The patient can name with reasonable certainty the side which first started bleeding, which is the side of the bleeding point. The quickest and easiest method for controlling the hemorrhage is to insert *nasal packing* into this side.

For this purpose tampons of long-grained cotton wet with 0.25 per cent neosynephrin hydrochloride or 1 per cent ephedrine hydrochloride in aqueous solution are employed. Each strip should be very thin and about 5 cm long. It is gently inserted into the nostril, no effort being made at the time to identify the actual bleeding point if it is not easily seen. The packing is left in situ for a few minutes while other similar packs are being made. The nasal packs already inserted are withdrawn and replaced. At such a time it may be possible to see the bleeding point, which in about 85 per cent of cases lies on Little's area of the septum. This is the area of anastomosis of four arteries and of their accompanying veins and is most easily designated as that portion of the septum which can barely be reached when the forefinger nail is placed in the nasal cavity on the septum and pushed backward and upward (in other words the area usually traumatized by patients in picking the nose). The vessel producing the freest hemorrhage from the anastomosis is the sphenopalatine artery although any of the vessels may cause profuse bleeding.

A small amount of cocaine (so as to make about a 1 per cent solution) may be added to the adrenergic solution already employed if one thinks that the bleeding point must be cauterized. A satisfactory cauterizing agent consists of chromic acid crystals made into a bead on a wire. Such a wire is heated until it is red hot in a gas flame. (The gas stove in the kitchen serves this purpose practically.) The tip of the heated wire is plunged into the chromic acid crystals which promptly melt into a bead which is used when cool. In cauterizing the bleeding point only the actual leak in the vessel should be destroyed. It is unwise to cauterize an area even as large as the little finger nail and the destruction of the mucous membrane over a diameter of 1.5 cm., as is sometimes done, produces unnecessary trauma. Such trauma may cause interminable crusting later.

Frequently the bleeding is so severe that cauterization is of little value. In this case the nose must be packed with either petrolatum gauze or boric ointment gauze. Ordinary sterile supplies of boric or petrolatum gauze prepared in any hospital operating room serve perfectly. Soft sterile gauze impregnated with boric ointment from which it can be made at the bedside and used if necessary. Strips about

the length of an ordinary cigarette are made but are compressed just as if a cigarette were compressed between two heavy objects. A number of such packs are prepared and are inserted from before backward upon the floor of the nose, one lying upon the other from above downward and making pressure between the medial and lateral nasal walls. Two strips are added to the packing after the bleeding has ceased and all the packs are secured externally by tying them together with silk string which is fixed on the dorsum of the nose with adhesive. An adhesive strap is placed over the packed nostril to prevent expulsion by sneezing. Aspiration of the packing is prevented by securing the string to the face.

Only the nostril which has bled is packed.

The last two strips are withdrawn 24 hours after having been placed in the nasal cavity and the remainder after 48 hours. Usually no further bleeding occurs.

Fibrin foam and fibrin film<sup>10</sup> offer interesting possibilities for use in epistaxis. Ely's placental extract has already proved its value when instilled upon nasal packs. Hemostatic globulin (Lederle) is an effective topical agent.

The principle of treatment is to control the bleeding point chemically, with a hemostatic agent, or by cauterization and therefore destruction, or by packing. In every case of nosebleed the blood pressure should be observed, the urine examined, and in middle-aged or elderly people unilateral persistent epistaxis requires an investigation for possible malignancy of the sinuses.

Blood loss is dealt with as in any surgical condition.

#### POSTOPERATIVE TONSILLAR HEMORRHAGE

The general practitioner may find himself faced with the problem of controlling hemorrhage from one of his own or a specialist's postoperative tonsillectomies. What shall he do?

When he is called by telephone and informed of the emergency he should order the patient's head to be kept high on several pillows, with an ice collar applied to the neck. Constant retching should be avoided and the throat and neck moved as little as possible. The pulse is to be observed frequently and recorded.

When the doctor arrives he will usually find a large blood clot in one tonsillar fossa or the other, or there will be a clot dangling from the nasopharynx—which means that it is the adenoid area and not the tonsillar fossa which is causing the emergency. If other than a very small amount of blood clot is allowed to remain in the healing area, further bleeding almost invariably occurs. This is true with so-called "primary" hemorrhage which occurs during the first 24 hours (usually the first 6 hours) or in the secondary hemorrhage which occurs usually on the fifth, sixth or seventh postoperative days. The large clot lends the patient only temporary assistance, by its contracture

the plug in the open vessel may be pulled out and further bleeding thus occur, or swallowing or retching may dislodge the clot. The grossly visible coagulated blood is therefore removed. A convenient means for accomplishing this is to use a suction apparatus with an ordinary metal throat suction tip if the patient is in a hospital, if at home, a tonsil sponge holder works well. A shrinking solution such as 0.25 per cent aqueous neosynephrin hydrochloride, 1 or 2 per cent aqueous ephedrine hydrochloride, or 1:1000 aqueous adrenalin hydrochloride is then employed. It may be sprayed into the area if no fresh bleeding occurs, but if there is oozing, it is applied with pressure on a tonsil sponge held by a sponge holder.

This must be followed by the use of an astringent or coagulant solution.

The usual astringent remedy at the Massachusetts Eye and Ear Infirmary is 20 per cent tannic acid in glycerin. After removal of the blood clot and application of one of the above adrenergic drugs, a tonsil sponge is soaked in the tannic-glycerin solution and held by means of a sponge holder or hemostat in the tonsillar fossa over the bleeding point for 5 minutes or more. If necessary, morphine is given preliminary to the foregoing treatment.

If these measures do not control the bleeding, No. 000 plain catgut sutures can be placed by means of a Henton needle and hook (Fig. 87). By taking small bites of tissue with this instrument bleeding can be easily controlled.

Good preliminary anesthesia is obtained by spraying the throat with 4 per cent cocaine containing 1:50,000 adrenalin hydrochloride. The injection of 2 per cent novocain with 1:50,000 adrenalin for anesthesia will frequently stop bleeding temporarily. This has the disadvantage of requiring the use of a needle which causes almost as much discomfort as the placing of the suture. General anesthesia for the control of postoperative tonsillar bleeding carries the risk of aspiration of blood clot and should be avoided except under special circumstances.

Patients sometimes become almost exsanguinated from persistent postoperative tonsillar bleeding. In every case the pulse rate and blood pressure must be watched carefully. The bleeding and clotting time are taken, together with repeated blood counts. Hylanone (vitamin K) subcutaneously, vitamin D and calcium are useful in selected cases. Fluids are given freely, parenterally if necessary. If the blood count drops below 3,000,000 red cells or the hemoglobin below 50 per cent the patient should be transfused.

Hemostatic globulin (Ederle) for topical application after removal of the blood clot is a useful coagulant. It is helpful also in the control of adenoid bleeding when used as nose drops. Placental extract is another good local coagulant. It is possible that fibrin foam,<sup>22</sup> which has been successful in a clinical trial as a coagulant in neurosurgery, may

later become valuable in throat surgery Care must be taken to prevent aspiration of this material<sup>13</sup>

**Adenoid Bleeding**—The control of adenoid bleeding in general requires measures similar to those described for postoperative hemorrhage complicating tonsillectomy In addition a *postnasal pack* is occasionally necessary This is applied by passing a small soft rubber French catheter through the nose into the oropharynx It is picked



Fig 87—Instruments for placing a suture in the tonsillar fossa Number 000 plain catgut is employed in the needle without twisting or knotting When the suture is placed the hook is a convenient instrument for securing and pulling the thread from the eye of the needle

up with a hemostat and brought out of the mouth A silk string is tied to the tip of the catheter as it emerges from the mouth and in turn the string is anchored to a small roll of sterile gauze of such size as to fill approximately the cavity of the nasopharynx The catheter is then withdrawn from the nose, pulling the silk string with it This, in turn, pulls the gauze pack into the nasopharynx The string is secured externally on the face, thereby anchoring the gauze in the

nasopharynx. By using two catheters it is possible to place one string through each nasal cavity and use the columella of the nose (adequately padded) as a means for securing the strings which are tied to each other.

Such a pack entails little or no risk of producing an acute otitis media if it is removed within twelve to twenty-four hours. If it must remain as long as seventy-two hours, the risk of such a complication is very great, even if the pack is changed during this time.

### NASAL FRACTURE

Nasal fracture cases are often referred to the specialist by the general practitioner because of fear of accepting responsibility for a poor cosmetic result. There is no particular reason why the general practitioner cannot reduce a nasal fracture just as satisfactorily as the specialist if a few simple principles of technique are clearly understood. X rays taken in the Waters position are valuable in showing the lateral displacement, while the lateral films show chiefly any posterior displacement. Properly taken x-ray films yield very valuable information as to the exact nature of the deformity which must be dealt with, and should be taken routinely whenever there is any question of a nasal fracture.

The cardinal point to be remembered in the reduction is that the nasal septum is almost invariably fractured along with the nasal bones and that the posterior displacement of both the anterior fragments of the nasal bones and of the septum causes interlocking with the posterior fragments, as if the down strokes of the letter 'M' were impacted against the upward strokes of the letter 'W'. Under gas oxygen it is possible, by elevating the "M" upward and forward from the "W," to free the impaction easily. Then very marked overcorrection of any lateral displacement in the opposite direction to such displacement should be carried out. *The whole secret of a good cosmetic result lies in overcorrecting the lateral displacement far beyond what seems to be a good position.* Thus, if the displacement is to the left, it should be corrected very far to the right, after lifting the fragments upward and forward. The fragments can then be gently molded into the best cosmetic position, but such fragments tend to assume the original deformity if the overcorrection described has not been adequate.

It is impossible to remove the impaction by manipulation of the external nose without placing a blunt instrument within the nose on one side or the other to assist in lifting the fragments. Such an instrument is placed intranasally about 5 to 8 mm. superior to the upper border of the nasal bone of one or the other nasal cavity, the instrument having been sterilized and covered at its tip with sterile vaseline or sterile boric ointment. A small straight blunt pointed hemostat used with its broad surface applied to the septum can be utilized,



but a broad, very blunt-edged septal dissector is the ideal instrument. Such an instrument is shown in Figure 88.

The entire procedure requires only a fraction of a minute. No dressing of any kind need be applied to the nose afterward. Postoperative nasal hemorrhage is almost invariably moderate and frequently absent if reasonable gentleness has been employed in the manipulation. Precautions should be taken to guard the patient against displacing the fragments during sleep by rolling over on his nose the first night postoperative. This precaution is unnecessary thereafter.



Fig. 88—An instrument useful in the reduction of a nasal fracture.

Postoperative x-rays may be taken two or three days after the reduction. The manipulation described above should be repeated if the position of the fragments is not satisfactory.

How late can a nasal fracture be so reduced after the injury and how early should it be reduced? The latest I have reduced such a fracture after injury is 13 days. The nose can be manipulated easily during the first 5 or 6 days but thereafter manipulation becomes more difficult. If there is a great deal of contusion about the nose the swelling may be allowed to subside somewhat before the reduction, although in general the sooner the reduction is done the better.

Lacerated wounds on the dorsum of the nose not infrequently convert a simple nasal fracture into a compound one, and in such a case the attending physician must exercise great caution to prevent infec-

tion as in any compound fracture Debridement, proper cleansing of the wound, sulfanilamide powder applied locally, avoidance of "tight" suturing and sulfonamide orally may all prove valuable

### ITCHING EARS

Itching in the ear is commonly caused by eczema whether of the dry or wet variety The following ointment will sometimes relieve the itching and improve the skin of the canal

- |   |                    |   |                |
|---|--------------------|---|----------------|
| R | Tinc. benzoin comp | } |                |
|   | Zinc oxide         |   | 1a 6 cc (3iss) |
|   | Petrolatum         |   | ad 30 gm. (3i) |
- Mix and make an ointment.  
Dispense box of sterile cotton tipped toothpicks.  
Sig. Apply to itching ear four times a day

Fungous infection of the external canal may simulate either weeping eczema or thin cerumen, it may cause the patient to think that he has a chronically draining ear The diagnosis is made by the usual laboratory methods related to fungous skin infections, as well as by the characteristic odor of the aural secretion and by the color of the discharge. (For example *Aspergillus niger* produces a black discharge, *Aspergillus flavus* produces a deep orange colored discharge, etc )

The following prescription is often helpful

- |   |                |                  |
|---|----------------|------------------|
| R | Salicylic acid | 0.65 gm (gr x)   |
|   | 70% alcohol    | ad 30.0 cc. (3i) |
- Mix and make a solution.  
Dispense dropper in bottle.  
Sig. Eight drops in ear four times a day

In both eczema and fungous infection of the external canal the following ointment may prove effective

- |   |                    |                  |
|---|--------------------|------------------|
| R | Phenol             | 0.33 gm. (gr v)  |
|   | White wax          | 0.33 gm. (gr v)  |
|   | Salicylic acid     | 0.65 gm. (gr x)  |
|   | Ammoniated mercury | 1.0 gm. (gr xv)  |
|   | Petrolatum         | ad 30.0 gm. (3i) |
- Mix and make an ointment.  
Dispense box of sterile cotton tipped toothpicks.  
Sig. Apply to ear canal four times a day  
(This medication is "strong" and is used cautiously at first)

Eczema of the skin of the external auditory canal may favor the retention of cerumen The penalty for "washing out the ear" for removal of wax in certain cases of eczema may be a weeping canal—continue for weeks or months (From the patient's point of view it is just as bad as stringing cerumen from a normal canal having an perforation in the drum and a dry middle ear— with intract-

toid and the disease process goes beyond simple soft tissue infection

It should be pointed out that in every case in which there is fluid of any nature in the middle ear, one expects to find similar fluid in the mastoid cells. Anatomically there is no barrier preventing this as the mastoid cells are in direct continuity with the air spaces of the middle ear.

If sulfadiazine has not been started before aural drainage began, the question arises as to whether it should be then employed. Since mastoiditis does not usually become established for about 8 or 9 days after the beginning of acute otitis media, the practitioner has a period of 3 or 4 days in which he may defer using such treatment. On the whole I prefer to proceed with sulfonamide therapy at once.

The patient usually asks the doctor how long the ear will continue to drain. The answer is that drainage lasts 5 days or less, or 2 weeks or longer, without sulfonamide therapy, but with such treatment the course is usually shorter. A draining ear which goes into the third week, regardless of any form of treatment, should be very carefully observed both clinically and by x-ray examination for surgical mastoiditis.

**Chronic Draining Ears**—This is a very complicated subject and only the briefest mention will be made of simple remedies. Aurists are able to obtain a dry middle ear in about 85 per cent of cases by conservative methods. One form of home treatment given the patient is to ask him to dry wipe the ear with sterile cotton-tipped tooth picks three or four times daily and to apply the following suspension:

Rx Weak Sulzberger's iodine powder	4 gm (5i)
70% alcohol	ad 30 cc (5i)
Mix and make a suspension	
Dispense dropper in bottle	

Sig Shake well before using, then instill 8 drops into draining ear four times a day after the ear has been dry wiped.

The patient is asked to lie on his good ear while the drops are being put into the draining ear, and to remain in that position for a few minutes.

The treatment of an acute exacerbation of a chronically draining ear always involves the risk of surgical mastoiditis and/or its complications. This type of patient should always be referred to an aurist.

#### SWIMMING IN RELATION TO EARS AND SINUSES

Does swimming account for any considerable proportion of aural and sinus infections? If so, how? It is axiomatic among otolaryngologists that swimming and acute upper respiratory infections ("nose colds" and sore throats) initiate the great majority of instances of acute otitis media and acute sinusitis. It is sometimes forgotten that

THE WORST SUCH CASES RESULT FROM THE COMBINATION OF SWIMMING (AND DIVING) PLUS ACUTE UPPER RESPIRATORY INFECTION, it is in this group that serious complications most frequently occur. A cardinal point in prevention, therefore, is to urge patients never to swim or dive in the presence of a head cold or sore throat.

Contaminated water is often blamed for middle ear and sinus infections, and undoubtedly this explanation is occasionally the correct one. The usual pathogenesis, however, is the transportation by lavage under pressure of the patient's own bacteria from the nasopharynx, nasal vestibules and anterior portions of the nasal cavities (approximately the posterior three fourths of each nasal cavity is normally sterile, or almost so) to the sinuses by way of the ostia or to the middle ear through the eustachian tube. The body chilling, which a large percentage of swimmers, especially thin ones, experience, and which is usually accompanied by a drop in body temperature, is probably a predisposing cause for infections following swimming. The greater the duration of such chilling (e.g., longer than half an hour), the more important it becomes, partly because of the nasal mucous membrane reflexes thereby produced (at first ischemia, later congestion).

If a patient has chronic purulent upper respiratory infection, the degree of risk in swimming is greater than is the case of a normal person, the greatest risk is entailed, however, by swimming while either an acute nose or throat process is present, or an acute exacerbation of a chronic process.

Diving merely increases all risks because of the greater hydrostatic pressure encountered.

A preventive technic in both swimming and diving is to BREATHE OUT THROUGH THE NOSE DURING EVERY INSTANT THAT THE HEAD IS UNDER WATER, thereby keeping water out of the nose and nasopharynx by means of positive air pressure. Inhalation in "crawl" strokes is through the mouth, as is inhalation at the end of a dive. Good swimming instructors teach these principles. The best prevention is to keep both the nose and mouth out of the water at all times.

An intact ear drum normally prevents middle ear infection from occurring through the external auditory canal. A perforation in the drum defeats this protection, as does the occasional occurrence of traumatic rupture of a thin membrana tympani in diving and striking the water with great force laterally. A 'dry' middle ear with a perforation in the drum may drain interminably after getting water in the middle ear from swimming or otherwise (e.g., irrigation of the ear for removal of cerumen) and water must be kept out of such ears. In chronic draining middle ears, an acute exacerbation of infection infrequently results. External otitis such as furunculosis, otomycosis and exacerbations of 'dry' into 'weeping' eczema may be related to swimming. It is therefore desirable to prevent water from

entering the external auditory canals so far as possible Olive oil on cotton wool in the concha and outer canal, and multiple bathing caps sometimes accomplish this purpose

The treatment of acute aural and sinus infections from swimming is the same as that outlined elsewhere in this paper for other such infections However, in this type of sinusitis<sup>12</sup> and otitis media, the staphylococcus is the usual offender, and as the disease process may be very severe, sulfonamide therapy should be started early

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# SEVEN COMMON AND IMPORTANT PROBLEMS IN THE MANAGEMENT OF HEART DISEASES AND DISORDERS

PAUL D. WHITE, M.D., F.A.C.P.\*

THE marked advance in our knowledge of heart disease during the past decade or two is now clearly reflected in our current therapy and I propose herewith to present seven cases illustrating the particular features of such treatment

## I ACUTE RHEUMATIC HEART DISEASE

A schoolboy aged 10 years living in Boston, is brought to the family doctor by his mother complaining of malaise and slight pain and soreness in knees, ankles, elbows and wrists of a week's duration, beginning 10 days following a rather severe sore throat. The tonsils were removed 3 years ago. There have been no important illnesses in the past.

The family history reveals the presence of valvular heart disease in a maternal aunt but is otherwise unimportant.

Physical examination shows a boy, rather slight in build, listless, and with a mouth temperature of 100° F. The nose and throat show no abnormality. There is slight tenderness but no swelling of knees and elbows. The heart is very slightly enlarged and there is present at the apex a moderately loud (grade 3) blowing systolic murmur heard in the axilla and at the lung bases but very indistinctly at the base of the heart. The pulmonary second sound is accentuated. The lungs and abdomen show no abnormalities.

The diagnosis is clearly that of acute rheumatic fever with slight enlargement of the heart and mitral regurgitation secondary to left ventricular dilatation, the result of rheumatic myocarditis. The possibility exists of a previous rheumatic infection which may have left either some cardiac enlargement or some mitral valve involvement. Physical examination 3 years before had, however, revealed no evidence of heart trouble.

The management of this case, which is an example of many similar patients encountered in New England, is dependent upon the intelligent appreciation of the rheumatic process. Rheumatism itself is widespread throughout the body but in this patient, as in so many others, it manifests itself particularly through cardiac involvement. X-ray examination of the chest if carried out in this patient would show a full-sized or slightly enlarged heart shadow, and the electrocardiogram would probably be normal except for a slightly elevated heart rate and perhaps slight prolongation of the P-R interval to 0.20 second and when the normal for this age should not be over 0.16 second. Myocardial rheumatism like acute rheumatic involvement in gen-

*Massachusetts General Hospital Lecturer in Medicine, Harvard Medical School*

eral, persists as a rule for weeks or months, and inasmuch as conservatism is in order, it is best to plan therapy lasting for a period of a minimum of 3 months following the discovery of this acute disease. Sometimes the process continues much longer than 3 months, for 6, 9, 12 or even more. Sometimes but not often it is much shorter, lasting only a few weeks.

*Bed rest* is the essential treatment so far as our present experience allows us to say with any certainty. Even when the patient feels quite well again he may show minor manifestations of persistent activity in the form of slight fever or increased leukocyte count or increased sedimentation rate, and so during the existence of such manifestations he had better be kept in bed. The reasons for such long bed rest are quite obvious. In the first place, bed rest is the rule and a wise one in general during any infectious process. Secondly, and probably even more important, such a course is especially advisable in this disease because of the frequently serious cardiac involvement. A heart already dilated and sometimes in mild total failure should not have imposed upon it the extra effort of its owner being up and around and the excitement of his having many visitors. The larger the heart resulting either from the infection or from unnecessary effort or from a combination of the two, the more permanently cardiac enlargement is likely to remain, and therefore, the worse the future. This is very important to remember during the period of convalescence when the child feels much better and is very anxious to get up and around. Good health and muscle tone can be quickly restored eventually in such children even though they may spend months in bed.

To aid in the convalescence of these children various *measures to improve their morale* and to gain their cooperation are in order. At the Massachusetts General Hospital the social service group working for the Children's Heart Clinic has done a very important service in the last decade or two by its pioneer work in establishing the In-Bed Club for children with all its appurtenances and various occupational therapy wisely planned and executed through the cooperation of the staff of social workers, nurses and physicians. Included in this cooperative group are the visiting nurses and the visiting teachers of whatever community the child lives in. Helpful items are the In-Bed Club badge, the In-Bed Club jacket, and the In-Bed Club magazine. Somewhat similar measures can be effected in private practice.

Drugs have been regarded in general as of little importance in this disease and have been used largely symptomatically. For joint discomfort and effusions into either joints, pericardium, or other serous cavities, the *salicylates* have been found very helpful, the commonest of which is acetylsalicylic acid (aspirin). Sodium salicylate with or without equal parts of sodium bicarbonate, and sometimes the application of oil of wintergreen externally, have been used for many

At one time, a generation ago, it was thought that the salicylates might act more or less specifically in controlling the infection and protecting the heart if large doses are given, for example, 100 to 150 grains daily by mouth in the acute cases in young adults or half that dosage or less in children. However, it was frequently found that, although the joint discomfort was relieved very dramatically by such treatment and the fever controlled, the infectious process itself might continue for weeks and months during the therapy. Hence it became customary to advise caution in the use of such drugs so that the evidences of the infection would not be masked and therewith convalescence terminated too soon.

Recently there has been a revival of interest in the possibility of a more or less specific effect of the salicylates by Coburn\* who has given the drug intravenously in his Naval Medical Service apparently quite effectively in a considerable group of patients with acute rheumatic fever. He has given doses up to 10 gm daily by infusions for 2 weeks, and has advised a new technique for measurement of the concentration of salicylates in the serum. It is still too early to say with certainty what the results will be. It is important to recognize that important toxic effects can be produced by massive doses of salicylates but it is also possible that the drug may have more than an analgesic and antipyretic effect.



than those in a countryside like New England is that in the tropics the hemolytic streptococcus is a much rarer cause of infection. Just how far a change of climate, or the use of sulfonamides prophylactically or at the time of the onset of infection with hemolytic streptococcus or the use of antistreptococcus vaccination may eventually help in the control of rheumatic fever we do not know, but it is true that individuals who live under better conditions have much less rheumatic fever and rheumatic heart disease than do those who live in poorer surroundings with crowding and inadequate diet, clothing and protection from infection.

## 2 SUBACUTE BACTERIAL ENDOCARDITIS

A young woman, 20 years old, with known rheumatic mitral valve disease (moderate regurgitation with little or no stenosis) has been ill for 2 or 3 weeks with unexplained fever and malaise. At first it was thought that she had the grippe but the persistence of the symptoms finally induced her and her family to seek medical help. Investigation reveals the presence, not only of a moderately loud apical systolic heart murmur with little or no enlargement of the heart, but also of a temperature of 101° F by mouth, a regular but somewhat accelerated pulse at a rate of 100, slight enlargement of the spleen, a few petechial hemorrhages on the arms and trunk, and slight clubbing of the fingers.

The clinical diagnosis is clearly that of subacute bacterial endocarditis, and this is confirmed by the fact that four out of six blood cultures taken in the course of the first week of study reveal the presence of *Streptococcus viridans*.

The heart itself is not a problem here except as it is the locus for superimposed infection on thrombi located on the valves and endocardium by the *Streptococcus viridans*. No attention to the heart per se, as a rule, is needed otherwise. The difficulty in this serious disease is that even after the organisms on the surface of the vegetations are cleared by chemotherapy, others growing deeply in the clots of fibrin are not easily reached, and so the disease may seem to recur or crop up again after it has been partially controlled, or the chemotherapy may lose its original effect. Fortunately, however, there is an attempt at repair going on in these cases from below, the organization slowly progressing into the clot itself. If this process can continue with the sterilization of the surface of the vegetations and clot underlying the surface, eventually a cure may be effected. Sometimes such sterilization is effective under present day treatment.

Prior to the practical introduction of the sulfonamides some 5 years ago the death rate from subacute bacterial endocarditis was very high, almost 100 per cent. By the use of the sulfonamides, in particular sulfapyridine and sulfadiazine, with or without heparin to help to prevent new thrombi from being laid down, the mortality was reduced somewhat, to a figure between 90 and 95 per cent. The treatment as recommended 2 or 3 years ago by the use of the *sulfona-*

*undes\** was as follows. An initial dose of 2 gm of sulfapyridine was followed by another 2 gm in 2 hours, following which 1 gm was given every 4 hours, until the blood level of free sulfapyridine had reached as near as possible to 10 mg per 100 cc. The dose was then adjusted to maintain this level for weeks.

During the past year new hope has arisen due to the trial of *massive doses of penicillin*. When smaller doses of penicillin were used 2 or 3 years ago there was little or no favorable result, but during the past 6 months or more penicillin in a dosage of 200 000 international units daily by vein or intramuscularly for a period of 2 to 3 weeks has resulted in the apparent control of the infection for a few months at least in approximately a third of the cases treated in this way. Hence, this patient described above should be, according to current experience, given the benefit of this new treatment for a period of 3 weeks, and then if the infection seems to be reasonably well controlled with disappearance of fever and the sterilization of the blood stream the drug may be discontinued, but the patient carefully followed with the resumption of similar therapy if there is a recurrence of the evidences of infection. Fortunately, in contrast to treatment with other drugs, especially with the sulfonamides, penicillin has shown little or no toxic reaction. The only disadvantage is a possible thrombosis in the injected veins or the precipitation of congestive failure in a few cases due to the amount of fluid that is administered to carry the penicillin. It is still too early to tell what the eventual outcome may be with this most recent penicillin treatment of subacute bacterial endocarditis. At least another year should elapse before we can speak with any confidence, at the present time, however the early results are encouraging.

The condition actually dates back to the age of 15 when there was a spell of extreme fatigue or palpitation or some such symptoms after an unusual strain or special episode. At that time the medical advisor may have told the family or the lad himself that he must avoid strenuous effort or perhaps that there was a little trouble with the heart. Following that episode at 15, there had developed in this individual a definite psychoneurosis, mostly an anxiety neurosis, with avoidance of any effort or strain that might tend to bring on a recurrence of these same symptoms that have now brought him to the Station Hospital. Hence, when this soldier was admitted to the Army he was in a relatively poor state of physical training with a considerable psychoneurosis which was easily discovered by careful and prolonged questioning.

Not infrequently there is in these patients an important family history of such or related troubles, and also not infrequently, there has been difficulty in social adjustments at home. If further careful examination is carried out, it becomes evident that there are a few unusual reactions, particularly a hyperventilation on relatively little effort, sometimes with excitement this hyperventilation induces in its turn a sense of dyspnea and symptoms resulting from an alkalosis. Also, it becomes evident that training for the original position of infantryman is likely to be a failure. In an investigation that we have been carrying on concerning this condition of neurocirculatory asthenia we have found it futile to attempt to train or retrain patients with neurocirculatory asthenia that is in any way marked.

The precise underlying cause and mechanism of the symptoms remain obscure, but their significance and the practical utilization of the knowledge already gained can be quickly applied in similar cases. In other words, it is important to recognize this condition either at the Local Board or Induction Station examinations or at any rate early in training so that the men with moderate or higher degrees of the condition can be rejected at once or those with lesser degrees of the condition placed in noncombatant positions where their services may be useful but where the symptom complex will remain at a minimum.

Drugs are of little or no avail nor are threats or rest treatment or anything else as yet discovered. Sympathetic reassurance and appreciation of the limitations, probably inborn but aggravated by environmental circumstances in early and recent life, are the foundations for adequate management of the condition even though specific treatment per se is as yet nonexistent.

#### 4 MALIGNANT HYPERTENSION WITH CARDIAC ENLARGEMENT

A woman, aged 40, has been having for some months bothersome headaches, easy fatigue and a little shortness of breath on such effort as climbing stairs which previously had not troubled her.

Physical examination discloses a rather nervous, somewhat overweight person, with good color and normal findings except for hypertension (systolic pressure 190 and diastolic pressure 140), moderate cardiac enlargement, slight diastolic gallop rhythm at the apex, and accentuated pulmonary second sound.

Fluoroscopic examination shows moderate cardiac enlargement with prominence of the pulmonary arc and increased lung hilus shadows.

The electrocardiogram shows slight to moderate left axis deviation with depressed S-T segments and inversion of the T waves in Leads I and IV.

The urine is normal except for slight reduction of specific gravity in the concentration test and a few casts in the sediment. The renal function phenolphthalein test shows slight reduction. The eyegrounds reveal grade 4 changes with marked modification of the arteries, a few hemorrhages, and some exudate.

It is evident that this patient is suffering from a marked hypertension particularly affecting the diastolic level, with important secondary effects on heart, arteries and kidneys. The heart is already in mild failure and if this strain goes unrelieved it is likely to increase the failure still more even though digitalis is given to afford some temporary benefit.

Because of the advance that has taken place recently in the therapy of hypertension including the possibility of reversing cardiac findings, this patient is referred to the hospital for the so-called *Smithwick hypertensive work-up* which includes the various routine methods of examination plus the reaction of blood pressure to posture, cold test and sedation. A pyelogram is found to be normal. The blood pressure at rest in the recumbent position measures 170 systolic and 120 diastolic. The systolic and diastolic pressures rise 10 mm each in assuming the sitting upright position and another 10 mm each in the erect position. The cold test which consists of the reaction of the blood pressure to the effect of immersion of the arm in water (at 3° to 4° C. for 1 minute) elevates the pressure to 190 systolic and 150 diastolic, and in the standing position to 200 systolic and 160 diastolic. The sedation test which consists of the effect of the action of amytal, 0.2 gm (3 grains) given at 7 00, 8 00 and 9 00 P M, reduces the pressure to 140 systolic and 90 diastolic during deep sleep.

This patient is thus suitable in all particulars for *Smithwick's splanchnic resection* except for the evidence of the advanced heart strain. Her age, the height of the diastolic pressure in relation to the pulse pressure which puts her in *Smithwick's* most favorable group which he calls Type 1, and her reactions to posture, cold and sedation all make her a favorable case for the more extensive lumbarodorsal sympathectomy which he introduced in 1940<sup>1</sup> and which he has carried on since with success. Where inadequate splanchnic resection in former days was capable of improving only 10 to 15 per cent of the patients, *Smithwick's* present method of neurosurgical treatment is successful in some 65 to 70 per cent of the cases and probably much more, even 90 per cent in well selected relatively young patients. The mortality has remained very low indeed even though there is a hazard in some patients who have had cardiac involvement. Naturally it is better to carry out the operation before such serious involvement exists. The patient is subjected to sympathectomy first

on one side and 10 days later on the other side. There is a slight drop in the pressure after the first operation and a marked drop after the second. This drop has been maintained for 4 or 5 years in the earliest cases successfully so treated.

In the patient under discussion above, the blood pressure one year after operation registers 130 systolic and 85 diastolic with a return to almost normal heart size and a return of the T waves in Leads I and IV of the electrocardiogram to a normal level.

This is an excellent example of reversible heart disease although, as noted above, it is far better to carry out the procedure before serious effects are found in heart, arteries or kidneys. There are still some failures but even when the pressure is not returned completely to normal there may be enough relief from the strain to allow subsidence of evidence of cardiac involvement, as shown by the electrocardiogram, for example.

The *technic of the operation* was outlined by Smithwick as follows:

It was found that adequate exposure of this entire region could be obtained by resecting the twelfth rib, through a hockey-stick incision. The upper portion of the incision is vertical, about two inches lateral to the midline, running up over the inner end of the eleventh rib. The lower portion curves laterally, one-half inch below and parallel to the twelfth rib. The sheath of the sacrospinalis muscle is opened vertically to below the twelfth rib, and dissection is then carried laterally following the skin incision through the deeper structures below and beyond the tip of the rib. The twelfth rib is removed from the transverse process to the lateral border of the sacrospinalis sheath. The twelfth intercostal artery, vein, and nerve are resected over a similar area. The diaphragm is divided from its lateral border to the spine, one inch below and parallel to the pleural reflection. The pleura is then separated from the thoracic cage up to the middorsal region.

The kidney then is readily exposed and inspected. An excellent view is obtained of the entire organ including its pedicle. The adrenal gland is readily seen and explored. The sympathetic trunk and paravertebral region are exposed from D9 to below L2. The great splanchnic nerve can be seen from its insertion in the celiac plexus upwards for virtually its entire extent, with its important branches running to the aorta above the diaphragm. The exploration having been completed, the desired portion of the splanchnic supply is then removed, the diaphragm resutured, and the wound closed in layers with silk technique. Intratracheal anesthesia is used. The operation is done in two stages between one and two weeks apart.

## 5 ANGINA PECTORIS DECUBITUS

A man, 50 years old, strong and robust, somewhat overweight, a former athlete, high-strung, and very busy in his professional life, first notices on a cold morning in the fall, while hurrying for a train, slight substernal oppression radiating a little to the left arm. This quickly subsides on resting.

Here is the commonest initial manifestation of coronary insufficiency due to atherosclerosis and narrowing of the coronary arteries with inadequate supply of blood to the myocardium of the left ventricle.

This symptom recurs more and more easily and somewhat more severely through the fall months. About the middle of December he is awakened about

by this same severe substernal pain. He gets relief in a few minutes after

sitting up in bed. He then sleeps the rest of the night comfortably. Three nights later he is again awakened by the same symptom. He is similarly troubled for the first time during a business conference while seated in his office the next day. He then consults his physician who finds no evidence of abnormality on physical examination. The electrocardiogram, however, shows low T waves in Lead I and slightly inverted T waves in Lead IV and in the precordial leads CF IV and CF V.

The diagnosis of angina pectoris decubitus is now in order. It is evident that an important coronary vessel has been affected and that the myocardium is inadequately supplied with blood as the result of coronary constriction which has not yet been compensated for by the development of a collateral circulation. The doctor wisely advises complete rest at home or in the hospital for the next few weeks, in bed or in chair (sometimes a chair position is much better than recumbency). There should be no constant moving about or activity such as that of taking a bath or a shower, or shaving, although bathroom privileges may be permitted if angina pectoris is not induced as a result.

This symptom of angina pectoris decubitus continues with little change for 3 weeks and then slowly but surely abates. After another month's time there are no longer any attacks at rest and the patient is able to do a moderate amount of exercise such as walking and stair-climbing without pain. After another 2 or 3 months even walking rapidly on a level causes no symptoms and the acute or subacute coronary insufficiency is at an end. The electrocardiogram becomes normal again. He has escaped evidence of actual myocardial infarction. Although he has not had any fever, leukocytosis or characteristic changes in the electrocardiogram indicating scarring of the heart, he has nevertheless been in serious hazard of life itself for a few months.

One cannot overemphasize the importance of a *rest cure* during periods of angina pectoris decubitus. It is just as important to treat angina pectoris decubitus by rest as it is an actual myocardial infarct. It is quite likely that as many deaths have occurred during periods of angina pectoris decubitus as during acute myocardial infarction or even more owing in part at least to the failure to restrict activities over that period of time. With recovery from this process however, the coronary circulation may become completely adequate and life may continue for many years. There is no difference in ultimate prognosis nowadays between angina pectoris decubitus and angina pectoris on effort. The expectation of life after the first symptom of angina pectoris is 9 to 10 years.<sup>2</sup>

Treatment other than rest is relatively unimportant. The *nitrites* are however of considerable value in the form of tablets of nitroglycerine 1/200 to 1/100 grain under the tongue as needed in prevention of attacks of pain or in the form of the more slowly

acting nitrites, namely sodium nitrite or erythrol tetranitrate  $\frac{1}{2}$  to 1 grain two or three times a day, especially at bedtime. Sometimes the combined use of nitroglycerin and one of the other nitrites is worth while. In a few cases *aminophylline* 3 grains three to four times a day in enteric-coated tablets acts beneficially and it may be used routinely if it helps and does not upset the gastro-intestinal tract. The occasional inhalation of *oxygen* or even long-continued inhalation of oxygen may help a little. *Papaverine* has been recommended by some writers but it has been of little value in many cases. *Radical measures* of treatment which include total thyroidectomy, the implantation of muscle or omentum into the pericardium, the production of pericardial adhesions, or even the simple methods of thoracic sympathectomy or paravertebral alcohol injections are rarely needed. Nor is adrenal radiation of any particular value. All these methods have sometimes been credited with improvement that is spontaneous and results from the natural evolution of an adequate collateral circulation.<sup>3</sup>

#### 6 INSOMNIA DUE TO LEFT VENTRICULAR WEAKNESS

A business man, 60 years of age, with a considerable amount of high blood pressure over a period of 4 to 5 years, has begun to notice shortness of breath on less and less effort and also has been bothered a good deal by insomnia. The insomnia has not been helped particularly by hypnotic drugs such as phenobarbital, nembutal and amytal. Even our old standby paraldehyde also fails. Occasionally in the night he becomes restless, sits up in a chair, and in that position is much more likely to sleep than when he returns to bed.

Physical examination shows a big, somewhat overweight man, with good color, normal breathing while seated during questioning but a little dyspneic after undressing for physical examination. There is no abnormal pulse in the neck. There is no edema of the extremities. The lungs are clear. The liver is not enlarged. The heart shows a maximal apex impulse in the 6th space, 10.5 cm to the left of the midsternal line and 2 cm beyond the midclavicular line. There is a slight diastolic gallop rhythm at the apex with accentuation of the pulmonary second sound. There are no murmurs. The heart rate is regular at 90. The blood pressure is 220 mm of mercury systolic and 120 diastolic. There is definite alternation of the pulse with a difference of 10 mm. between the stronger and weaker beats.

Fluoroscopic examination shows the heart moderately enlarged with a prominent, slightly dense aorta, prominence of the pulmonary arc, and increased density of the lung hilus shadows. The lungs are clear otherwise.

Electrocardiography shows normal rhythm at a rate of 85 with considerable left axis deviation and inverted T waves in Lead I and in the precordial leads at the apex and to the left thereof.

The urine is acid with a specific gravity of 1.020, a slight trace of albumin, no sugar, and occasional casts in the sediment. The red and white blood cell counts are normal. The hemoglobin is normal. The Hinton reaction is negative. The vital capacity is 3 liters, normally it should be at least 4.5 liters for his build.

The diagnosis is obvious: hypertensive heart disease with left ventricular enlargement, weakness and early failure. Because of our experience with similar cases in the past and the realization that one of the most important causes for insomnia in such patients is pulmo-

nary congestion, particularly in the recumbent position, we treat this patient with *diuretic drugs* and *absolute rest* as well as with digitalis which he has already been taking in adequate amounts with only partial benefit. With more complete rest for two weeks, and especially as the result of intravenous *mercurial injections* (mereupurin 1 to 2 cc.) every 2, 3, or 4 days for several doses, this patient not only improves in every way objectively with the restoration of normal vital capacity and disappearance of his dyspnea on slight effort, but *he also begins to sleep again with ease, even without hypnotic drugs*.

Since insomnia and nervousness are occasionally two of the most obstinate and annoying symptoms associated with left ventricular weakness, it is of great importance to recognize this association and to treat such patients with rest and diuretic therapy as well as with digitalis.

To supplement the mercurial injections, *ammonium chloride* in the dosage of 1 gm (two 7½-grain enteric-coated tablets) four times a day is often very helpful. Also it is often of great importance to restrict the fluid intake to a maximum of 40 ounces in 24 hours. For a satisfactory check on the progress of such a case it is helpful to have three daily records as follows (1) intake and output of fluid, (2) weight, and (3) vital capacity.

## 7 TROUBLESOME AND CRIPPLING ATTACKS OF CARDIAC ARRHYTHMIA

A professor aged 65 has for several years been bothered by short paroxysms of irregular tachycardia proved two or three years ago to consist of auricular fibrillation. Otherwise there has been no evidence of heart disease although at times the blood pressure has been slightly elevated (160 systolic and 100 diastolic). Except for the arrhythmia the electrocardiogram has been normal. The attacks have followed unusual fatigue, nervous strain, or sometimes a hearty meal with the excessive use of tobacco following it.

Quinidine sulfate in the dosage of 6 grains at 2 hour intervals for one, two or three doses, has invariably been followed by a cessation of the attacks and on occasion when he has felt a few premature beats and has been tired he has taken a few doses of quinidine sulfate 3 grains, 2 or 3 hours apart, as a prophylactic. During the past 6 months, despite the successful use of the quinidine sulfate in treatment, the attacks have come more and more frequently so that now they occur every day or two and greatly disturb his routine life, for during the attacks he is more or less upset, nervous, is uncomfortable (though without cyanosis and dyspnea) and has increased urination.

Physical examination shows little or no abnormality.

The patient is now put on quinidine sulfate regularly in the dosage of 3 to 6 grains three or four times a day. For a few weeks this therapy is helpful but then there begins again a rapid recurrence of the paroxysmal auricular fibrillation.

This situation is best treated, we have found, by the omission of quinidine and the institution of full digitalization and its maintenance. The auricular fibrillation is thereby established permanently and the ventricular rate kept under control so that there are no more disturbs-



ing attacks The irregularity of rhythm itself, although noticeable as palpitation at first, becomes gradually imperceptible to the patient, and except for taking one dose of digitalis daily (1 to 1½ grains of the powdered leaf in pill or tablet form) the patient lives a perfectly normal life Permanent auricular fibrillation with rate well controlled by digitalis, in the absence of any important heart disease, can be supported by the heart, and by the patient too, in perfect comfort for many years It is not as satisfactory a rhythm as a normal one but the clinical state of the patient is greatly benefited by this change which offsets the hazard of paroxysmal arrhythmia The institution of digitalization and its maintenance is even more indicated in cases with frequent paroxysmal auricular fibrillation in the presence of organic heart disease due either to mitral stenosis or to other factor If thyrotoxicosis is the cause of such arrhythmia, the obvious treatment is subtotal thyroidectomy which as a rule cures the arrhythmia

### CONCLUSION

I have presented seven fairly common and important clinical problems involving cardiovascular symptoms and signs that face the general practitioner Perhaps the most hopeful aspect of these cases is the change in the point of view that we have slowly developed in the past decade or two Heart disease and disorders, formerly regarded as permanent and hopeless, are now in many cases being rightfully recognized as reversible conditions, at least in their earlier stages

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# PRESENT DAY TREATMENT OF ESSENTIAL HYPERTENSION

DAVID AYMAN, M.D.\*

In the present paper on the treatment of essential hypertension, I shall present not only those methods of therapy which I have found effectual under critically controlled observation, but also point out those drugs, diets and methods which have no adequate scientific basis for use. Preceding the discussion on treatment, it is best to review briefly the different causes of hypertension.

## THE VARIOUS CAUSES OF HYPERTENSION

By far the commonest cause of elevated blood pressure is essential hypertension. However, about once in fifty times the patient in whom you find an elevated blood pressure has an acute or chronic glomerulonephritis, as evidenced by albuminuria, hematuria, and other common signs. Perhaps one in a few hundred patients with hypertension has enlarged congenital polycystic kidneys as disclosed by palpation of the abdomen or by x-ray. On rare occasions tumors of the adrenal gland may cause acute paroxysms of marked hypertension associated with rapid pulse and pounding headache. Just as rare a cause of hypertension is coarctation of the aorta; here, hypertension of the upper extremities only is found as a result of a congenital narrowing of the thoracic aorta with its accompanying low or normal blood pressure in the lower extremities and a scalloped erosion of the lower borders of the ribs. Unilateral or bilateral pyelonephritis may in exceptional instances cause hypertension. Basophilic adenomas of the pituitary are another rare cause. Then there are the cases found in the toxemias of pregnancy, and in urinary obstruction due to an enlarged prostate or renal calculi. Brain tumor with marked intracranial pressure may rarely cause hypertension. Finally, a rare case of "Goldblatt-Page hypertension" may be found, due to renal infarct, arteriosclerotic occlusion of the renal arteries, and so forth. However, the two types of hypertension most frequently encountered are hypertension due to nephritis and, most often, essential hypertension.

## DIAGNOSIS OF ESSENTIAL HYPERTENSION

This disease is called 'essential' or 'primary' hypertension because, after ruling out the above less common causes of an elevated blood pressure, we are left with no organic abnormality adequate to explain

\*From the Department of Medicine Tufts Medical School and the Beth Israel Hospital.

\*Assistant in Medicine Tufts Medical School. Associate Visiting Physician, Beth Israel Hospital.

it The frequent organic findings of an enlarged heart, thickened arteries, abnormalities in the ocular fundi, slight albuminuria and red cells in the urine are the result and not the cause of the elevated blood pressure. On the other hand, we all see patients in their early thirties with elevated blood pressure in whom none of these abnormalities are found. Such patients are really in the early stage of essential hypertension. Rare postmortem studies on such a person who has died from an accident or another unrelated cause reveal no abnormality. Biopsies of the kidneys of hypertensive patients also frequently show no abnormality.<sup>1</sup> The clinical diagnosis, therefore, depends on the finding of an elevated blood pressure without evident cause.

**Blood Pressure Levels in Untreated Essential Hypertension**—Whenever at any age a blood pressure above 140 mm of mercury systolic or 90 diastolic is found either frequently or constantly, especially but not necessarily in the absence of a rapid pulse, then the diagnosis of a pathological elevation of blood pressure must be made. When a blood pressure only slightly above 140 systolic and 90 diastolic is found frequently in a person who had a parent with hypertension, cerebral hemorrhage, or who met an early sudden death, then the slight elevation of blood pressure is even more certain to be early essential hypertension. This early diagnosis is still further aided by noting the patient's personality. It is not necessary to have psychiatric training to observe that the patient has excessive emotional reactions or physical drive, or both. This emotional hyperactivity is evidenced by a serious planning nature, a quick temper, or a supersensitive nature. The physical hyperactivity is expressed by unusual speed at work, talking, eating, walking and other activities. Most patients with hypertension have this type of personality.<sup>2</sup> Some have this type of personality to such a degree that they seem always as if on the bursting point, and are described as "hyperthyroid types." However, not all persons with this type of personality have or will have hypertension. A combination of mild, inconstant or constant elevation of blood pressure, the hypertensive personality, and a family history of the disease makes the diagnosis of early essential hypertension very likely. Most of these early cases have no symptoms and are discovered on routine physical examinations.

The blood pressure levels both in the early and the more advanced cases vary tremendously.<sup>3</sup> We all see young men who have been rejected by the armed forces because of hypertension, yet who in our office have little or no elevation of the blood pressure. This illustrates that patients in all stages of hypertension respond to emotional stress by elevations of the blood pressure from the original level, whether that original level was 130 systolic or 230 systolic, and that these elevations due to excitement will disappear when the stimulus is removed. The statement of the patient that he does not feel excited may be correct, but it does not alter the fact that he really is under great



home and clinic in a patient with known hypertension for fourteen years and only slight organic changes. In the figure it is seen that the initial readings of blood pressure, as indicated by a dot in a circle, have varied during the past fourteen years from 210 to 136 systolic, and from 120 to 72 diastolic. If we observe the vertical solid columns, which represent the variations of blood pressure during a 10 to 30 minute rest period in the clinic, we also find marked fluctuations. In the boxed-in area from March 7, 1944 to April 13, 1944, the daily home blood pressure readings of this patient are seen to be markedly lower than the clinic readings during this same period. A detailed study of such a group is to be published separately.

### THREE GROUPS OF SYMPTOMS IN ESSENTIAL HYPERTENSION

Although the diagnosis of essential hypertension depends entirely on the presence of an elevated blood pressure and not on certain symptoms, the treatment frequently concerns itself with symptoms. There are three kinds or groups of symptoms in essential hypertension, each group requiring distinctive treatment.

**Psychoneurotic Symptoms**—In 1931, Pratt and myself showed that many of the symptoms of patients with essential hypertension closely resemble those seen in patients with psychoneurosis without hypertension.<sup>5</sup> Closer study of our patients revealed that they really were suffering from a psychoneurosis as well as hypertension. The psychoneurosis was the result of emotional conflicts to which hypertensives are prone, owing to their highstrung personalities. The tendency of such hypertensive patients to be easily hurt and unusually sensitive, together with their serious planning natures all aided in the production of headaches of all sorts, dizziness, weakness, insomnia, constipation, diarrhea, urinary frequency and bitter tastes. Such symptoms really resulted from their inability to adjust to the problems which confronted them or which they thought were going to confront them. To list the symptoms in this group really amounts to naming symptoms referable to all parts of the body—all those seen in any "nervous" patient.

**Vasospastic Symptoms**—Since essential hypertension is associated with constriction of the arterioles over the entire body, even in the absence of a psychoneurosis, it seems likely that symptoms may be produced solely by varying degrees of constriction or spasm.<sup>6</sup> Yet it must be noted that a blood pressure as high as 250 to 300 mm systolic may exist for years without a headache or other symptoms. Here we invoke the explanation that people vary in their sensitivity to disease processes. At any rate, we often find severe headaches, dizziness, nervous tension without basis, spells of flushing and pallor, all intense and prolonged. The type of headache is variable but prolonged and intense. Great rises in blood pressure with headaches, convulsion and momentary pareses appear on the probable basis of vascular spasm.

**Organic Symptoms.**—In this group are the easily explained symptoms of shortness of breath due to cardiac enlargement and failure, nocturia due to renal damage, angina pectoris due to arteriosclerotic involvement of the coronary arteries, cardiac asthma and cerebral hemorrhage, all on the basis of organic involvement of the body. This organic involvement in turn results from the damage of the arteries and arterioles by the prolonged elevation of the blood pressure. It is important to distinguish the sighing difficult breathing in the psychoneurotic symptom-group from the true shortness of breath in heart disease, the nocturia due to insomnia from that due to renal function impairment, the vague pains and skin sensitivity around the apex of the heart found in psychoneurosis from the true anginal midsternal pain of coronary disease.

#### THE TREATMENT OF HYPERTENSION

Many patients with a blood pressure of only 160 mm systolic may have marked symptoms, while patients with systolic readings above 300 mm may be free of complaints. I have often found it helpful in practice to separate the treatment of the symptoms from that of the blood pressure itself.

**Treatment of "Hypertensive" Symptoms—1 Psychoneurotic Symptoms.**—When the diagnosis of this group of symptoms is made, the treatment should consist of psychotherapy and the use of the sedatives. By psychotherapy I do not mean psychoanalysis in its Einsteinian complexity but merely a careful inquiry into the emotional problems of the patient, and an explanation to the patient that his or her symptoms are due to these problems rather than the blood pressure elevation itself. An attempt then to make the patient change his poor reaction to these problems will at once start him, if he is cooperative on the road to recovery from his symptoms.

Drug therapy in patients with this group of symptoms should accompany psychotherapy. The simple sedatives are best. In the case of patients who become fatigued from night after night of broken sleep adequate doses of phenobarbital (0.1 to 0.2 gm [ $1\frac{1}{2}$  to 3 grains]), or chloral hydrate (0.6 to 1.3 gm [10 to 20 grains]) or amital (0.1 to 0.2 gm [ $1\frac{1}{2}$  to 3 grains]) are given night after night until adequate sleep results in a return of pep and vigor. The complaints of headache, fatigue and so forth will also improve markedly.

When patients with a psychoneurotic background become aware that they have a high blood pressure, the emotional concern over their blood pressure often becomes the sole cause of their psychoneurotic symptoms. In this large group placebo, prescribed with an air of great assurance, will lower the blood pressure and relieve the symptoms. In 1939 I obtained relief of symptoms in 82 per cent of such patients by the use of colored dilute hydrochloric acid given with

Hundreds of articles have appeared on the successful treatment of hypertension by many different methods and drugs, none of which have any specificity. They all have one thing in common—the enthusiastic treatment of a worried patient. In this light it is essential to mention drugs which have received wide advertisement but have no value. Among these are garlic preparations (e.g., Allimin), mistletoe (e.g., Hepvisc), and watermelon seed. Also of no value are various drugs, such as Theominal and Iocapral, which have been combined with phenobarbital. The various xanthine diuretic drugs like aminophylline and theobromine have no value in the treatment of blood pressure or its associated symptoms. When combined with phenobarbital, the sole value in the preparations is in the phenobarbital. The latter is obviously tremendously cheaper to use alone.

2 *Vasospastic Symptoms*—Chief of the vasospastic symptoms are headache and dizziness, the former being by far the more common. Sometimes these severe prolonged headaches respond to large doses of sedatives as above outlined, or to periods of rest and vacation. However, the drug most useful for the relief of these headaches is potassium thiocyanate. The dosage and method of use of this valuable potent drug will be outlined later under the treatment of the blood pressure elevation itself. In those cases which do not respond to the thiocyanates, lumbar puncture will occasionally afford relief.

3 *Organic Symptoms*—The treatment of shortness of breath due to heart failure, and other symptoms of organic origin, is discussed elsewhere in this symposium.

*Treatment of the Elevated Blood Pressure Itself*—I have found on repeated observation<sup>8</sup> that the blood pressure level of the hypertensive patient will drop progressively from his first visit to the clinic to at least his fifth or sixth visit. This drop occurs either without any treatment at all or with treatment with pink or white placebo tablets. Practitioners who do not take complete cognizance of this easily demonstrable fact will erroneously believe that the drug given the patient at the first visit was the cause of the drop in the blood pressure. Figure 90 illustrates this fact. Useless drugs like garlic and mistletoe exert their nonspecific and only effect during the first few visits of the patient, and have no effect if placebos are given at these early visits, to be followed by the above inactive drugs.

Only two practical methods are now available for lowering the blood pressure itself—the use of potassium thiocyanate and the operation of sympathectomy.

**POTASSIUM THIOCYANATE**—The best drug I have found which will lower the blood pressure level to an important extent is potassium thiocyanate. However, it is clearly a drug that must be administered under unusually careful observation.<sup>9</sup> Its toxic dangers can now be avoided by determining from time to time the amount of the drug in the blood.<sup>10</sup> Since there are no other worthwhile treatments available,

this drug should be employed with these precautions. First, one should arrange with his local laboratory or hospital for the chemical determination of the blood levels. This chemical test is easy for any laboratory that makes blood chemistry studies such as the determination

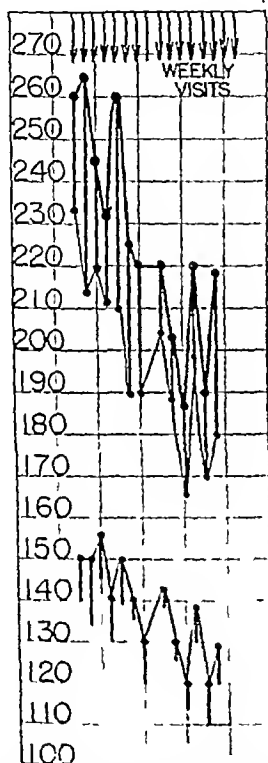


Fig. 90.—Blood pressure variations at weekly visits over a 4 month period. The upper black dots are the initial readings at start of a 4 month treatment. The lower black dots are the initial readings at start of a 4 month rest period. The vertical black column beneath the dot represents the blood pressure during the rest period.

the blood nonprotein nitrogen. The dosage of the drug varies with each individual because the rate of excretion of the drug by the kidneys varies in different patients.

Use of Potassium in Treatment.—The first



cardia which result in prolonged weakness until the body adjusts itself

The type and extent of sympathectomy vary in different parts of the country. Our experience strongly favors the two-stage bilateral lumbodorsal sympathectomy of Smithwick.<sup>13</sup> However, sterility of the male will result from this extensive type of operation, although normal sex life may otherwise be maintained.

The actual *indications* for operative interference are not yet completely defined. Sympathectomy of course should never be considered an emergency operation. If the disease is so far advanced that immediate treatment is imperative, the chances are that no results will be obtained from the operation or that the patient is too poor a risk for surgery. Patients with renal failure, fixed specific gravity, or congestive failure are obviously poor risks. Operation should not usually be done in patients who have normal sized hearts as seen on the 7-foot x-ray screen, who have normal electrocardiograms, normal ocular fundi, and normal renal function and urine unless blood pressure levels are at tremendous heights over a long period (one year or more) of careful observation.

It must be emphasized that brief preoperative hospital observation, as practiced throughout the country, is not an adequate basis for determining the advisability of an operation and certainly not for evaluating drops in blood pressure short of drops to normal levels. The period of preoperative hospital observation is notoriously a period when the blood pressure levels are at their worst, due to inradicable nervous tension. Comparison of such false preoperative levels with postoperative levels is of no value unless the postoperative level is absolutely normal—which is not a usual finding. The physician who sees his patient month in and month out for several years, who carries out proper studies of heart, kidneys and fundi from time to time, and who makes careful records of blood pressure levels at all visits is best qualified to determine whether the patient's condition is stationary, slowly progressive, or rapidly progressive. The finding of a stationary state without demonstrable damage of the heart, brain or kidneys is a reason for maintaining the status quo. If, however, it was noted in 1943, for example, that the heart and electrocardiogram were normal, but in 1944 the heart has increased in size on the 7-foot x-ray plate, or the electrocardiogram shows left ventricular strain, then an indication for operation seems established. The development of inconstant or constant albuminuria or decrease in the concentrating ability of the kidneys and the finding of constricted vessels or hemorrhages in a previously normal ocular fundus are reasons for advising operation. Finally, a persistently rising blood pressure level in a patient observed over an adequate period—months to several years—is another indication for recommending operation.

In Figure 91 are presented pre- and postoperative blood pressure

levels in a moderately successful case treated by operation. In Figure 92 an unsuccessful result is shown. In both charts we show clinic levels of blood pressure, as well as home levels of blood pressure as determined by the patients themselves. In Figure 91, the moderately successful case, it is seen that there are two different levels of blood pressure, depending on whether the readings are taken in the clinic or at home. It is these different levels that cause confusion in interpretation of all therapeutic results. Certain it is that in a successful case as charted in Figure 91 the patient still has variable hypertension of mild degree if readings are taken before rest. If readings had

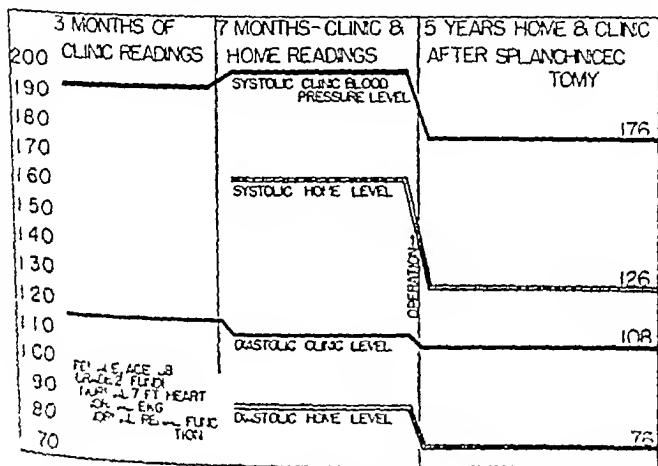


Fig. 91.—Blood pressure levels for 10 months before and 5 years after bilateral splachnicectomy. These are average levels. The solid black line indicates clinic levels. The double line is the home level.

observing the blood pressure before prescribing the diet Likewise, restriction of salt and spices is of no value

**DRUGS THAT ARE OF NO VALUE**—I have already mentioned that other than the thiocyanates, and the simple sedatives in very large doses, there are no drugs that will lower the blood pressure *and keep it low* The nitrites are vasodilators but their effects are very brief Adequate doses of the slow acting nitrites, such as erythrol tetranitrite, cause severe headache The very slow acting nitrites, such as mannitol hexanitrate, either have no effect at all or only a slight effect None of the diuretic drugs are of value for hypertension Preparations of garlic (i e, Allimin), mistletoe (i e, Hepvisc), watermelon seed, liver

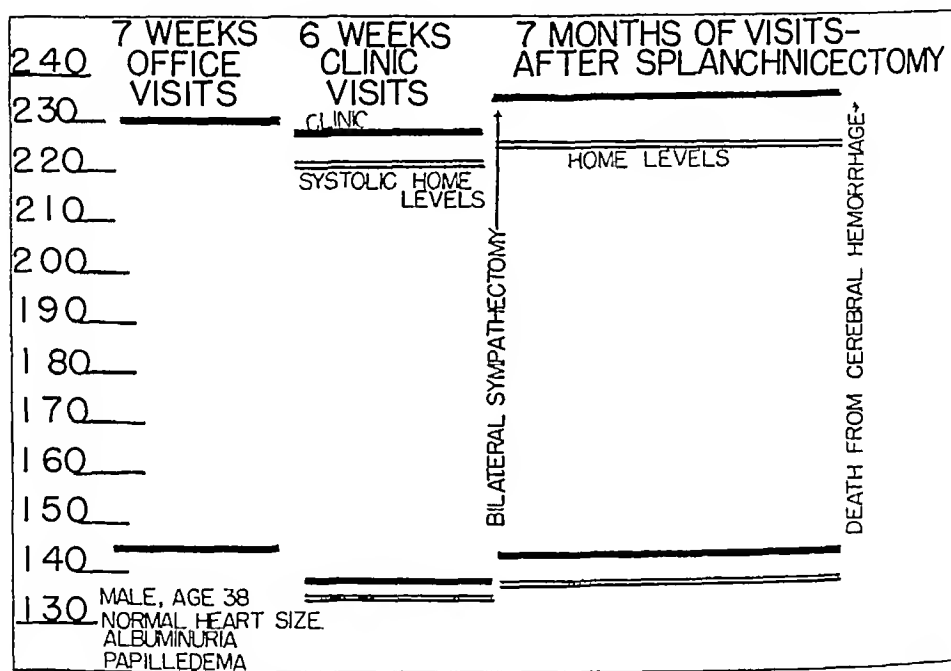


Fig 92—Blood pressure levels for 3 months before and 7 months after bilateral splanchnicectomy Otherwise as in legend for Figure 91

extracts, vitamin A, all have no effect and no scientific data to back them up<sup>14</sup> It is well to remember that many of the so-called advertising-medical journals, which are sent gratis to doctors, contain advertisements of drugs that have no scientific therapeutic basis and which are not accepted for advertising in recognized medical publications Such data should be consigned to the wastebasket When an effective new hypotensive drug is discovered it will be rapidly publicized through reliable channels

### SUMMARY

The treatment of essential hypertension often involves the treatment of the symptoms as distinct from the elevated blood pressure

The diagnosis and treatment of the three groups of symptoms are discussed. The successful treatment of the blood pressure by thiocyanates and by sympathectomy is described. Methods and drugs that are of no value are indicated.

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# FUNCTIONAL GASTRO-INTESTINAL DISTURBANCES

CHESTER M. JONES, M.D.\*

THAT emotional disturbances and states of nervous tension can be responsible for somatic symptoms is a fact that is generally accepted by the majority of practicing physicians. Too frequently, however, the practical application of such a concept in the actual handling of problems as they are presented by the patient is lacking. The steadily increasing tempo of modern life, with its stresses and strains, is reflected in the vast majority of histories that can be obtained in office and hospital practice.

In no system of the body is there a more obvious and at times more dramatic manifestation of the close relationship between organic symptoms and psychological disturbances than in the gastro-intestinal tract. Alterations of function on the basis of psychological factors, affecting as they do secretory, motor and absorptive processes, can be easily determined by adequate study and particularly by a careful history. It is still true that most erroneous diagnoses are due to the lack of a meticulous history, rather than to the lack of other forms of clinical investigation, particularly those relating to laboratory procedures. Too often diagnosis and therapeutic measures are predicated upon an attempted assay of innumerable and frequently unnecessary laboratory studies, when a really thorough history would provide the logical diagnosis and indication for therapy. It goes without saying that in patients complaining of serious symptoms adequate studies are needed in order to rule out the more serious forms of organic disease, but many times such studies fail to reveal the true cause of the patient's disability and suffering.

## PATHOLOGICAL MECHANISMS

Innumerable papers have been written on the subject, and the profound observations of men like Weir Mitchell, Pavlov, Alvarez and many others point clearly to the mechanism underlying a large proportion of digestive tract symptoms. The actual visualization of alterations in gastric or intestinal physiology during periods of abnormal nervous stimulation has been clearly described by various authors. Beaumont, in his classical studies on gastric physiology, observed striking changes in the appearance of the stomach under various emotional and mood changes. Intense hyperemia, "aphthous patches" in the stomach and increased mucus secretion were frequently noted.

More recently the very excellent studies of Wolff and his collab-

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\* Clinical Professor of Medicine, Harvard University, Physician, Massachusetts General Hospital

orators on another patient with a gastric fistula demonstrated even more clearly the very definite relationship between gastric physiology and the function of the higher nervous centers. Extreme pallor of the gastric mucosa and diminished secretion accompanied states of fear or anxiety, whereas extreme resentment was usually associated with an intense increase in the vascularity of the mucous membrane and with increased gastric secretion.

Similarly, White and Jones demonstrated by sigmoidoscopy analogous changes in the appearance of the normal mucosa of the rectum and sigmoid following overstimulation of the parasympathetic nervous system. Cholinergic drugs even in moderate doses produced in normal individuals such extreme occluding spasm of the sigmoid that the passage of a sigmoidoscope was rendered impossible. Under these circumstances all normal vascular markings were obliterated, and diffuse marked hyperemia was noted, with a definite increase in the secretion of mucus. An extreme example of such a physiological change was observed in one normal individual who became suddenly embarrassed during the sigmoidoscopic examination, with an almost immediate change in the color of the mucosa from a pale salmon pink to a bright red color. The change was so intense that it was described as a "rectal blush." Such observations indicate clearly the close integration between the autonomic nervous system and higher emotional centers and the actual functioning of the digestive system.

The term "functional disease" is not particularly precise in its application to various clinical problems. It is undoubtedly true, however, that the exaggeration of normal physiological responses as described above can readily form the basis of important symptoms that create diagnostic and therapeutic difficulties. The actual borderline between organic disease and a functional disturbance is so tenuous and so shifting that it is frequently all but impossible to state that no organic disease exists. The symptoms, physical findings, and roentgenologic and sigmoidoscopic abnormalities that can be demonstrated in patients with so-called mucous colitis are a good example of such a difficulty. Nearly all experienced observers are agreed that this condition does not represent a true colitis. Yet in innumerable instances there is not only a history of repeated attacks of intense abdominal pain, but one can easily demonstrate a tender, palpable sigmoid on physical examination. Because of the intensity of the symptoms and the apparent definiteness of physical findings, many ill advised operations have been performed only to find no organic disease. The secretion of mucus in such instances is at times amazing and the mucous casts so clearly resemble tissue that not infrequently both the patient and the physician are alarmed by their appearance. Such phenomena certainly are not organic disease in many instances and possess many of its clinical and symptomatic characteristics.

**Spastic Muscle Spasm Mimicking Organic Disease** — An extreme exam-

ple of the intense smooth muscle spasm that can occur under periods of extreme emotional stress was seen in the following case

An elderly man of 74 years was subjected to an abdominal operation because of recurrent attacks of diverticulitis of the lower sigmoid. The predominating element in the entire clinical picture was one of intense anxiety, which increased to a state of abject fear on the day of operation. Because of the age of the patient and his general physical condition, a low spinal anesthesia had been chosen for the particular operation in question, thus leaving the patient still in possession of his faculties when he reached the operating table, in spite of fairly heavy doses of sedatives.

On opening the abdomen, a hard, avascular tumor was observed involving the antrum and pylorus. Inasmuch as a careful x-ray study preceding the operation had shown no evidence of disease of the stomach, the exploring surgeon was extremely surprised and felt that there had been a possible error in diagnosis and that there might be an infiltrating carcinoma of the stomach which had not been recognized. The operation on the sigmoid proceeded, however, and after about 30 minutes it was noted that the pale, hard tumor of the stomach had completely disappeared and that the entire antrum and pylorus were not only normal in color but of normal consistency. It was undoubtedly true that the intense pylorospasm occasioned by fear of surgery was responsible for this curious phenomenon.

Such intense spasm undoubtedly occurs in many clinical conditions and, as a rule, is the occasion for extremely painful sensations. In the gastro-intestinal tract, localized spasm is apt to occur at or near the sphincters or in the narrower portions of the alimentary tube. Thus the cardiac end of the esophagus, the pylorus, the ileocecal junction and the sigmoid are sites where localized spasm frequently occurs with major symptoms. Anatomical defects, although not constituting actual organic disease, are also trigger points where focal disturbances may occur which form the basis of patients' complaints. Thus esophageal diverticula, para-esophageal hernias, Meckel's diverticula, diverticula of the large bowel, and minor areas of narrowing due to inflammatory adhesions may serve as the basis for focal changes in the vascular bed and local smooth muscle tone as the result of abnormal stimulation of the autonomic nervous system. In most instances the distressing symptoms resulting from such irritable foci do not require surgical treatment. Rather, the control of the individual, with his numerous reactions to the ordinary or extraordinary wear and tear of daily living may provide the most logical and the most satisfactory therapeutic approach.

**Gastro-intestinal Bleeding of Functional Origin**—Most physicians visualize the concept of smooth muscle spasm, with or without focal disease, as a basis for chronic symptoms. It is less commonly understood that at times associated changes occur in the local blood supply of the mucosal lining of the digestive tract in areas of spasm, which may simulate an inflammatory process and may even result in minor bleeding episodes. These changes have been visualized and described in detail in well illustrated articles by the various authors mentioned

above. The following clinical examples may serve as illustrations of the foregoing discussion

### CASE REPORTS

**CASE 1**—The patient was a 56-year-old married woman with a history of previous operations for subdeltoid bursitis, malposition of the uterus, and trifacial neuralgia over a period of approximately 15 years. Some months after a ventral suspension of the uterus (1919) the patient had a severe attack of lower abdominal pain without any preceding symptoms. There was no nausea or vomiting. Physical examination was negative and there was no elevation of temperature. She was seen by both a medical advisor and a surgeon, who decided that no operation was necessary but were unable to make an immediate diagnosis. Hypodermic injections of morphine were given with symptomatic relief.

A few days later the patient passed a very large amount of mucus by rectum, and a diagnosis of mucous colitis was made. Following that episode there was a constant recurrence of left sided abdominal pain, always associated with the passage of typical loose stools with large amounts of mucus. These episodes seemed more or less to correspond with periods of fatigue or prolonged nervous tension. During the ensuing years occasional studies were made of the entire gastro-intestinal tract, but no evidence could be obtained of any local disease. During the years 1925 to 1931 the patient's symptoms were less severe and were more easily controlled once a relatively smooth diet with antispasmodic and mild sedatives were employed.

In 1930 the patient began to be bothered by attacks of severe substernal oppression, with a feeling of tightness radiating up to the throat and what was described as local esophageal cramps. When these symptoms occurred there was apt to be a return of the bowel symptoms. The substernal distress occurred somewhat more frequently and was more intense during the following months, and at times, after eating the patient experienced extreme distress under the region of the xiphoid and a feeling as if she had eaten a very large bolus of food. Following a rather fatiguing Christmas and New Year period, her symptoms increased and were described as follows: (1) difficulty in swallowing, with a marked feeling of constriction at the lower end of the sternum (2) epigastric distress just under the xiphoid, going to the precordium and (3) extreme breathlessness. The patient recognized clearly that these symptoms might be brought on by any acute emotional disturbance or by fatigue. With the increase in symptoms suggesting esophageal disease, the colonic symptoms diminished in intensity. Finally a very distressing attack of substernal, precordial distress occurred, associated with extreme difficulty in swallowing. This attack came on shortly after the death of a close friend.



somewhat by psychiatric advice and somewhat by the use of sedatives and antispasmodics, with the result that x-rays taken in 1933 revealed no esophageal spasm. During the year 1932 there had been periods when it was necessary for the patient to take nitroglycerin as a means of enabling her to swallow adequate amounts of food. It was of interest that at this time the bowel symptoms were essentially nonexistent. The year preceding these x-rays had been a particularly distressing one on account of various incidents, such as prolonged sickness in the family and anxiety.

Finally, an interesting episode occurred in the year 1933 at the outset of an ocean voyage to which the patient had looked forward with a good deal of pleasure. In preparing for the voyage she became tense and unduly tired, and shortly after embarking had definite colonic symptoms and passed black tarry stools. There was no associated diarrhea and no fresh blood. For psychological reasons x-rays were not taken on her arrival in Europe, but on her return to this country adequate studies were carried out, which apparently ruled out any form of disease of the gastro-intestinal tract at any level. From 1933 to the present time no further episodes of tarry stools have occurred, although from time to time there have been attacks of substernal pressure, dysphagia and breathlessness, and periods of typical mucous colitis.

*Comment*—This case is of interest in relation to one subsequently to be mentioned in that it combined symptoms of smooth muscle spasm with probable vascular changes in the bowel productive of actual bleeding. No absolute proof was obtained as to the source of the bleeding, but in comparison with examples given below it seems reasonable to suspect that there was not only intense spasm but also intense hyperemia at some level of the digestive tract, resulting in capillary oozing. In this particular case the relationship between emotional disturbances and striking gastro-intestinal symptoms was always obvious. The first episode in 1919 simulated an acute abdominal attack and only after careful consultation was surgical intervention avoided. After the nature of the symptoms became more apparent, measures calculated to relieve local spasm and to enable the patient to live at a satisfactory emotional level were employed with varying degrees of success.

As is true in many instances, more than one level of the gastro-intestinal tract was involved. At times the esophageal spasm was so intense that it actually necessitated a sharp modification in diet, forcing the patient to take merely liquid food in small amounts. Repeated studies were necessary before the fear of organic esophageal obstruction was finally ruled out. The symptom of breathlessness was undoubtedly of nervous origin and will be commented upon again. It was entirely comparable to the paroxysmal episodes of intense sighing so frequently seen in overreactive, hypersensitive individuals. It is of interest to point out that on numerous occasions in this particular individual over the entire period of many years, symptomatic relief was frequently obtained by the use of nitroglycerin, a drug that is still not used with sufficient frequency in the handling of gastro-intestinal complaints.

CASE II.—The patient was a physician's wife, aged 55 years, who was admitted to the hospital because of nausea, heartburn, vomiting, peristaltic unrest and loss of weight, the symptoms being of 10 years' duration. Her past history was important because of the evidence of overreaction to excitement, emotional difficulties, and the like as shown by the fact that she vomited as a child after going to the circus. Her symptoms became aggravated 10 years before admission after the death of her husband, for whom she had constantly grieved. Physical examination, except for underweight, was entirely negative. Examination of the entire gastro-intestinal tract by x ray revealed no abnormality.

During the patient's stay in the hospital there were long periods of crying, which represented the obvious reaction to anxiety uncertainty, extreme loneliness and frustration. Only after prolonged reassurance, some sedation and a gradual increase in diet was it possible to eliminate nausea and vomiting. On discharge the patient was eating a fairly adequate diet. Her story is of interest in the present discussion because one year before her admission to the hospital, immediately after attending the funeral of a dear friend, she had had an attack of acute diarrhea, with day and night movements, mucus in large quantities, and after 24 hours the passage of blood, over a period of 3 days. Endoscopic examination at that time and subsequently failed to show any source of the bleeding in the anal canal or in the rectum or rectosigmoid.

During the year following her discharge from the hospital the patient had numerous relapses, with a return of upper gastro-intestinal symptoms. These coincided with emotional outbursts in every instance. At the end of this period she returned to the hospital at which time she exhibited a new symptom, namely extreme breathlessness and at times overbreathing, with actual tetany. Reassurance and a gradual reorganization of her life, combined with regulation of diet and smoking and the periodic use of antispasmodics, gradually resulted in improvement in symptoms and a gain in weight. No further episodes of bleeding occurred in the next 6 years.

*Comment*—A careful analysis of this patient's history at the time of each hospital admission revealed that his bowel symptoms were very definitely associated with periods of very profound anxiety, overwork and real fatigue. These factors were much more marked at the time of the first admission than four years later, but it is interesting to note that on the second hospital admission he was having, in addition to occasional bowel disturbances, vasomotor disturbances of tachycardia, excessive paroxysmal sweating, and flushing similar to the menopausal symptoms experienced by his wife at the same time. The latter volunteered the information that during her pregnancy the patient had vomited as much or more than she. At an insurance examination just prior to the second hospital admission at a time of unusual stress, sugar had been found in the urine, but subsequent fasting blood sugars and sugar tolerance tests revealed nothing abnormal. In other words, this patient also represented a hyperreactive type of individual with symptoms involving several systems but most striking as related to the gastro-intestinal tract.

**CASE IV**—A housewife of 46 years entered the hospital with a story of gradually increasing lower abdominal distress associated with the passage of hard, inspissated feces and rectal blood and mucus. After about 3 weeks of these symptoms she noted an increase in rectal discharges, many of which consisted in nothing but mucus and blood. Just prior to admission to the hospital, because of the use of milk of magnesia she was having six to eight bowel movements a day, with the frequent appearance of fresh blood in the stools and an associated loss of 11 pounds in weight. Her previous history was negative, except for the fact that she had always been a very emotional, overconscientious, introspective individual, who in spite of her marriage had been more closely attached to her mother than to her husband.

A complete physical examination was absolutely negative, aside from hyperactive reflexes, moist skin and dilated pupils. Examination of the anal canal was normal. Sigmoidoscopy revealed extreme hyperemia of the rectum and rectosigmoid, with superficial bleeding areas but no true ulcerations. The walls of the bowel were extremely contractile so that almost occluding spasm was produced by attempts to sponge the mucosa. Complete gastro-intestinal x-rays failed to reveal any evidence of organic disease. There was no evidence of any other systemic disturbance.

With sedation, a smooth diet and reassurance, the symptoms gradually subsided and the patient was discharged, to return 3 months later, at which time sigmoidoscopy showed no evidence of bleeding, although the sigmoid was still extremely spastic and hyperemic. After the second examination rectal symptoms disappeared completely and there was no further bleeding for some months.

Shortly thereafter, however, the patient began to complain of frequent paroxysms of sighing and inability to get a deep breath, with a feeling of choking and constriction around the neck as though "a valve had been suddenly shut off." Palpitation, sweating and giddiness occasionally accompanied these episodes. One such attack had occurred when she and her husband were starting off on a week-end excursion, and the appearance of symptoms had necessitated their return home to the close proximity of the patient's mother. Physical examination in the office was negative, but at the end of the examination the patient suddenly gasped, choked and called for help, desiring her husband and the physician to hold her up in order to prevent her falling over. Her husband, who was an extremely excitable individual, was very much alarmed, and his apprehension

increased hers, although it was quite obvious that the attack had all the earmarks of being hysterical in nature. It was of incidental interest that a white blood count done at this time was elevated, with a value of 14,000 cells.

The patient was immediately hospitalized and was studied thoroughly from the point of view of trachea, lungs and esophagus. All of these studies were negative both x ray and otherwise, and a throat consultant was unable to find any evidence of bulbar palsy, recurrent laryngeal nerve pressure, or local disease in the throat, pharynx, hypopharynx or larynx. Although there was no elevation of temperature and no evidence of any infection either on physical examination or urinary studies, the white blood count remained moderately elevated during this hospital admission. She was seen by a psychiatrist, who felt that the diagnosis was that of anxiety state with some hysterical features. At the time, the patient was anxious to discuss surgical interference for spasm of the larynx, an indication of the extreme apprehension under which she was living. She remained in the hospital for a period of two weeks and then returned home, for the time being relieved of all symptoms.

In reviewing the previous hospital and office studies in this case, it is interesting to note that a transient elevation of white blood count had been noted on previous occasions, without any evidence of infection whatever. Several months later a letter from her home physician related that there had been a return of her previous intestinal symptoms, with bowel frequency and the passage of some mucus and blood. These symptoms cleared up under appropriate treatment but on their disappearance there was again a return of the episodes of severe choking and difficulty in breathing. During the acute episodes her white blood count was noted to be at a level of about 12,000. Her home physician gradually gave her adequate reassurance, and for the following year and a half she was relatively symptom free. At the end of this time there was again a return of the bowel difficulties, with the passage of blood and mucus and associated episodes of difficult breathing.

*Comment*—A careful analysis of the entire history revealed that aside from the evidences of obvious emotional instability, no positive findings were made except that of a hyperemic, extremely spastic sigmoid which oozed blood in slight amounts on the slightest trauma associated with wiping gently with a sponge or on the passage of hard fecal material. The nature of the emotional difficulties became exceedingly clear during the period under which the patient was observed and was associated with two factors (1) real anxiety over her husband's health and financial affairs, and (2) a constant deep urge to be with her mother even at the expense of leaving her husband, to whom she appeared to be devoted. These episodes of emotional conflict invariably precipitated either the intestinal or the upper respiratory symptoms of which she complained. Inasmuch as she was followed over a period of 3 years there is little reason to believe that the leukocytosis was anything more than an unusual expression of a natural response to psychological unrest. Such a mechanism has been carefully studied and reported by various observers, including Garvey and his co-workers.

#### GENERAL COMMENT

The foregoing examples illustrate clearly the important relationship between the higher emotional levels and the functioning

of the gastro-intestinal tract or other systems. They are of particular interest because of the evidence of bleeding from the gastro-intestinal tract that occurred as a result of profound emotional experiences. It is of the utmost clinical importance that such an explanation for digestive tract bleeding should be accepted only after the most thorough studies and prolonged observation. Failure to exclude any form of organic disease capable of producing bleeding would at once invalidate any conclusions as to the "functional" nature of the symptom. In these cases, however, the individual patients were followed over a sufficient period of time and had sufficiently adequate repeated studies to warrant such an assumption. It is probable that the bleeding represents merely an exaggeration of the normal physiological response of one or another portion of the digestive tract to excessive stimulation. Such stimulation could come from an irritable focus at any level in the nerve pathways from the endings of the autonomic nervous system in the bowel wall to the higher centers. In these instances there seemed little doubt that abnormal emotional states produced periodic changes in the gastro-intestinal tract by means of stimuli carried over the pathways from the higher levels through the hypothalamic area to the final autonomic fibers. The instances of acute respiratory embarrassment associated with evidences of change in gastro-intestinal tone and vascularity are of some additional interest. The transient episodes of leukocytosis are also of interest and are probably analogous to the leukocytosis observed during drug withdrawal in morphine addicts.

#### TREATMENT

Once adequate studies have been performed and the nature of the cause of the symptoms is determined, therapeutic measures can be simply outlined, although they are difficult of performance. The fundamental principles to be followed are those to be employed in any unstable, overreactive individual. Whether or not intensive *psychotherapy* is indicated is dependent upon individual circumstances. More frequently than not the family physician who knows the patient and his surroundings best is in the best position to provide reassurance and stability. Artificial *regulation of living habits*, with adequate attention to periodic rest and regularity of living, is frequently an essential maneuver.

In the face of gastro-intestinal symptoms nonirritating foods form the basis of any dietary control, but *dietary measures* in themselves are far from adequate unless combined with the effective handling of the individual in question. *Antispasmodics* and *sedatives* offer additional help in the control of individual episodes or over long periods of time. For acute episodes, very often the repeated administration of *nitroglycerin* is extremely helpful in relieving the pain or discomfort incident to smooth muscle spasm. Over a long period of time *atropine*

or its derivatives or synthetic spasmolytic drugs are frequently of great benefit. In the case of atropine or belladonna, it is important to point out that nothing but tolerance doses are effective. Too frequently minimal or "safe" doses are employed, with no physiological effect whatever.

Only by a combination of all of these therapeutic measures over long periods of time can individual patients be brought under control and freed from the discomfort of such distressing symptoms as those described.

# THE TREATMENT OF THE PATIENT WITH AN UNCOMPLICATED PEPTIC ULCER

EDWARD S EMERY, JR, MD \*

THE treatment of patients with uncomplicated peptic ulcer has three objectives (1) relief of symptoms, (2) assisting the ulcer to heal and (3) prevention of reactivation after healing has taken place. The therapeutic procedures which are available for accomplishing these purposes may be divided into three categories (1) treatment of the local condition, (2) treatment of the patient's general health, and (3) education of the patient concerning the nature of his disease.

Judged by the late results, treatment is successful only if therapy includes all these points. Except in the mildest cases, treatment of the local condition alone provides only temporary relief of symptoms. Although a spontaneous remission of the disease occurs in a few individuals while under local treatment, there are many other patients in whom the ulcer does not respond satisfactorily. Naturally, every patient is desirous of obtaining relief from his symptoms and so this factor is of great importance to the individual. However, clinically, it is too often misunderstood and its significance exaggerated. Because a patient is asymptomatic is no evidence that healing is taking place. This is well illustrated in the patient who has kept completely free of distress by frequent feedings and alkali for weeks or months and is confident that his ulcer, at long last, has become just a memory. This hope fades quickly upon stopping the local treatment and he finds himself once more plagued by all his former symptoms and again subject to the restrictions of his disease. If healing is to be assured, it is essential to treat the patient's general condition.

After the ulcer has healed, reactivation may take place if there is allowed to develop the same circumstances under which the ulcer originally became active. The incidence of recurrences will be decreased only by education of the patient concerning the nature of his disease and those factors which are known to influence its course. In the actual treatment of a patient, local and general treatment and education will go on concomitantly. However, it is easier to discuss each category separately.

## LOCAL TREATMENT

Local treatment is of two kinds, medical and surgical. Medical treatment aims to (1) reduce trauma, (2) decrease spasm and (3) reduce the gastric acidity.

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\* Senior Associate in Medicine, Peter Bent Brigham Hospital, Instructor in Medicine, Harvard Medical School

**Reduction of Surface Trauma**—Reduction of surface trauma may be accomplished by starvation, tube feeding and bland diets. The value of *bland diets* which were originally prescribed empirically has been demonstrated experimentally by Ivy<sup>1</sup> and their use is indicated provided that the diet is well balanced as regards protein, carbohydrates and fat and contains sufficient calories and vitamins.

Although *starvation* and tube feeding are advocated routinely by some physicians, this procedure seems unnecessarily severe as most patients do well without the use of such rigorous therapy. Whether the patient is started on a graduated scale of feeding such as the Sippy regimen employs or on three full-sized meals of bland foods depends upon the irritability of the stomach. It is desirable to prescribe normal sized and well-balanced meals as early as possible, provided the stomach will tolerate them, since many patients with ulcers are poorly nourished.

**Treatment of Spasm**—Spasm about an ulcer interferes with the flow of blood to the involved area and may delay the healing process. Antispasmodics and the relief of nervous tension are indicated. Of the several drugs that are on the market, *atropine* is as efficacious as any and should be given to the point of physiological tolerance. *Heat* applied to the abdomen to ameliorate gastro intestinal spasm will produce the desired effect in 98 per cent of the cases and is indicated in the early days of therapy. Treatment of nervous tension will be discussed more fully later.

**Control of the Gastric Acidity**—There is less agreement on the role that *neutralization of the gastric acidity* plays in the treatment of peptic ulcer than any other phase of therapy. The most valid argument against it is that ulcers heal spontaneously without any change occurring in the acidity, and this is held as proof that neutralization is not essential for healing to take place. Furthermore clinical experience teaches that neutralization of the gastric contents may relieve all symptoms from an uncomplicated ulcer and yet the ulcer does not heal. The proponents of neutralization point to the wealth of animal experimentation which demonstrates beyond reasonable doubt a relationship between the gastric acidity and the development of an ulcer and to the clinical evidence in support of such a relationship. Patients are seen clinically who never get more than temporary relief or a partial treatment until complete neutralization of the gastric contents is accomplished. In addition, there is the clinical observation that rarely if ever does a peptic ulcer develop in patients who cannot secrete hydrochloric acid.

In the final analysis, the therapeutic role of neutralization should be judged by the benefits which result from its use. Because healing takes place without it, is no reason to condemn such treatment or to excuse for failure to take advantage of it as a useful adjunct in the treatment of therapy. The situation may be likened to the use



of digitalis in heart disease All patients with heart disease do not require digitalis, as many will become compensated on rest alone However, one does not withhold digitalis in these cases if improvement can be hastened or made more lasting by its use No one would deprive a lame man of his crutch simply because it is possible for him to walk without it

Likewise, granting that the milder cases of ulcer do not require neutralization, there are others in whom improvement will take place more rapidly and be more permanent if neutralization is employed This is particularly true of patients with a marked hypersecretion, as opposed to a so-called hyperacidity The titratable acidity is of little value in determining the immediate response to treatment or the ultimate prognosis unless the free acidity is 80 or more <sup>2</sup> The volume of secretion as determined by the Bloomfield method is much more useful Patients with rates above the normal figure of 15 cc per minute usually respond poorly to treatment This is certainly true when rates of 3 cc or more per minute are encountered Such cases will respond more quickly and, in general, much more satisfactorily if complete neutralization of the gastric contents is obtained

One of the first steps in the treatment of any patient is to decide whether any neutralization is to be attempted, whether partial or complete neutralization and the type of neutralizing agent to be used

The most frequently employed neutralizing agents today are sodium bicarbonate, calcium or magnesium carbonate, calcium phosphate, bismuth subcarbonate, magnesium trisilicate and aluminum hydroxide Each of these has its advantages and disadvantages and will be the drug of choice for certain situations

*Sodium bicarbonate* acts the most quickly of any, gives the most rapid relief and is frequently liked best by individuals with a hyper-irritable stomach Its disadvantages are a low neutralizing value per unit of weight and rapid absorption, with the resulting tendency toward the development of alkalosis The greatest disadvantage is the increased secretion of hydrochloric acid which follows its employment and for this reason it is definitely contraindicated for patients with hypersecretion

The *carbonates*, *phosphates* and *bismuth subcarbonate* are virtually interchangeable as therapeutic substances in the treatment of ulcer They have a greater neutralizing value than sodium bicarbonate and less tendency to produce alkalosis However, their use is followed by an increased secretion of acid although not to the same degree as with sodium bicarbonate *Magnesium trisilicate* is a pretty good neutralizer and its use stimulates little if any increase in secretion The amount which can be prescribed is often limited by its laxative effect.

*Aluminum hydroxide* has certain qualities not possessed by any of the others Given in sufficient quantities, it decreases the gastric acidity through its astringent effect <sup>3</sup> Absorbed only slightly by the body

and because of its amphoteric action, aluminum hydroxide does not produce alkalosis. Its slow and moderate neutralizing qualities are offset by the fact that the amount prescribed does not have to be limited through fear of alkalosis. If given in sufficient amounts, it is the best medicament for patients with hypersecretion. Not only can complete neutralization be established, but the amount of secretion will be reduced, thereby converting some of the most severe cases to a less resistant state. Its advantages lie in treating the severe case for whom complete neutralization throughout the 24 hours is desirable. The patient with a marked hypersecretion continues to secrete acid long into the night. By bathing the mucous membrane with aluminum hydroxide throughout the 24 hours a marked decrease in secretion will develop and the continuous secretion will disappear within 7 days. This continuous medication is possible only in a hospital or with a nurse in attendance who can awaken the patient for medication every hour of the night. Three weeks are required to accomplish the same results if the drug is taken only during the waking hours. Unfortunately, a few patients do not tolerate the drug well and cannot take it intensively. If given in small doses and only occasionally throughout the day it has no advantage over any of the other alkaline medicines. Moreover, the greater rapidity of action of the others will produce more rapid relief. The choice of the neutralizing agent therefore depends upon what one is seeking to accomplish, the facilities for administering the therapy and the type of patient one is treating.

Surgery as a means of local treatment of the uncomplicated ulcer is indicated if the patient cannot or will not follow an adequate medical program. For all practical purposes, it will be needed for the more severe or resistant type of case. The mild case can be easily controlled with medicine. When surgery is contemplated one should remember that the more severe the disease, the more it resists surgical medicine of permanently changing the local conditions and is, therefore, primarily of use for those patients who, for temperamental or economic reasons, cannot follow a satisfactory medical regimen. Most patients requiring surgery will need a radical resection. With less radical operations, the development of a jejunal ulcer is probable.

#### TREATMENT OF THE PATIENT'S GENERAL HEALTH

Like all chronic diseases for which no specific cure is available, the cure of the patient's general health is important.

General health is based on eliminating those factors which are known to accompany reactivity of an ulcer. These are (1) emotional factors, (2) general debility and fatigue and (3) intestinal tension. Contrary to popular belief there is no evidence that diet, per se, has any relation to a recurrence of activity. And rest is indicated for the fatigue and nervous tension which

nearly all patients harbor during an active phase of the disease. A period of rest in bed should be urged upon every individual in the beginning of treatment. Most patients who deny the need of rest when the subject is first broached, are convinced after a few days in bed that they are very much in need of such rest. Most of these persons will relax better away from home and a few days in the hospital is desirable whenever possible. *Mild sedatives* given throughout the day help the individual to relax. Phenobarbital 0.015 gm ( $\frac{1}{4}$  grain) every 4 hours works well and small doses give more desirable results than large ones. The duration of bed rest will depend upon how quickly the patient responds, but in many instances 5 to 10 days will suffice. This period of time is more convenient for many patients who do not feel able to devote 3 or 4 weeks to bed rest which some of the older regimens demanded. Moreover, this length of time is usually enough to adjust the local medical treatment to the patient's needs and to educate the patient to care for himself after leaving the hospital.

During this time, any foci of infection which is amenable to treatment can be given the proper attention.

#### EDUCATION OF THE PATIENT

Any treatment which is to be more than temporary must include education of the patient concerning the chronic nature of his disease, that there is no known cure for it, and that future results will depend more upon him and what he does than all the surgery and medicine which he may receive. It should be impressed upon him at the very outset that the physician can only tell him how he can control or live with his ulcer. He must be made to understand that no physician can make the ulcer conform to any mode of living which he chooses.

The relation of *nervous tension*, fatigue and infection to reactivation must be explained and the methods of prevention discussed in detail. It is not uncommon to encounter antagonism when this subject is first mentioned, but when the patient realizes that our restrictions do not interfere with his business life, and will make him a more effective individual, he will usually cooperate. Observation reveals that most patients expend an extraordinary amount of useless energy through failure to plan their activities. Caution the patient against undue haste and nervous tension. Advise a sufficient amount of time for dressing, eating breakfast and so on so that he can get to his place of business without any sense of pressure. Stress the value of short periods of relaxation throughout the day. The Army knows that it can march a body of men farther and more efficiently if a short rest period is allowed every hour. What is true for the muscular system is also true for the nervous system. Mealtime should be one of relaxation rather than tension and rapid eating. Rapid automobile driving

produces an expenditure of nervous energy entirely out of proportion to the few minutes it may possibly save and should be frowned upon. Outline a daily program for the patient which will assist him in living a more desirable existence.

The debilitating effect of *infection* should be explained and the need for preventing upper respiratory infections should be emphasized. It should be pointed out that a certain amount of nervous tension alone, or an ordinary infection alone, may not be sufficient to lower the patient's resistance to a point where the ulcer becomes active, whereas, a combination of the two may be just enough to bring a return of symptoms. The prevention of general *fatigue* by well timed vacations when they can be taken, an adequate amount of sleep which for most persons is a minimum of nine hours, and a period of rest in the middle of the day when it is possible to obtain it will serve to mitigate the development of fatigue.

This seems to be as good a time as any to discuss the matter of *smoking* and *drinking*. There can be no question that tobacco and alcohol are contraindicated theoretically and, to some extent, by clinical experience. Practically, is it better to forbid the use of these substances or allow them in moderation? I have found it difficult to get patients to forego these pleasures for the rest of their lives and because I have been unable to demonstrate that their use in moderation does any harm I advise total abstinence only while the ulcer is active. After healing has occurred, the patient is permitted 10 cigarettes a day or their equivalent. No alcohol is to be taken on an empty stomach, but a weak drink may occasionally be consumed during or after a meal. These rules do not deprive the patient of some social pleasures which, in my experience, they are more prone to follow than if they are forbidden ever to indulge.

This period of education can go on concomitantly with advice about diet and other medicinal procedures until such a time as the ulcer has healed and the patient is free of symptoms. The patient should be encouraged to return at regular intervals in order that the physician's influence will continue to be exerted toward a sound regimen.

#### TREATMENT OF THE INDIVIDUAL CASE

The art of treating peptic ulcer depends upon applying the necessary type of local treatment to any given patient. Care of the general health and education of the patient to the nature of his disease should be applied to all. One should not attempt to standardize the local treatment, the choice of which should be guided by the severity of the individual case. Too little attention has been given to this point by most physicians are accustomed to take it into consideration in the case of other diseases. One cannot accurately classify every patient. It is possible to recognize many of the severe cases and many of the mild ones. I have learned to recognize types of patients who

are always resistant to treatment. They have a severe grade of pain and frequently suffer from distress in the middle of the night. They show an unstable autonomic nervous system as manifested by a moist skin, particularly of the palms, and they have a tendency to flush easily. They often exhibit the typical ulcer diathesis, have a slight build and thin features with a pointed chin. They are often underweight and report an inability to gain weight. In the very severe cases the patient suffers from a hypersecretion as determined by gastric analysis. In this regard, we are interested in the amount of secretion rather than in the titratable acidity, a high acidity being of less significance than a high acidity combined with a large volume. Therefore, the thin, highly nervous patient who is having frequent and severe pain, particularly at night, and who is found to have a hypersecretion, falls into the severe class.

On the other hand, in the mild case the patient has less pain and is less subject to distress at night. The periods of freedom from symptoms tend to be longer than in the severe case and a hypersecretion does not occur. The patient is more likely to have a normal weight and a normal nervous system. This group can usually be recognized easily. The need for evaluating the severity of the disease is obvious because it is not necessary to treat a mild case by a radical form of therapy, and conversely, it is ineffective to treat a severe case by an inadequate therapy.

Mild cases will do well on almost any good regimen and can be ambulatory from the beginning. Being mild, the ulcers heal more rapidly and the distress is easy to control during the active phase. During the active period the patient will receive three meals of bland food, with milk once between meals and alkali three to five times a day to relieve symptoms. These measures will be adequate if the general treatment is carefully followed out. After healing has occurred, a normal diet should be given but the general treatment must continue.

In moderately severe cases more intensive treatment is required. A period of bed rest is indicated and some sedation should be prescribed. The use of the *Sippy regimen* depends upon circumstances, particularly the available opportunities for accurately carrying out the regimen and the social and economic status of the patient. However, let me repeat that relief without complete neutralization of the gastric juice will mislead the patient concerning the behavior of the ulcer and accomplishes nothing in healing the lesion. To obtain complete neutralization with the Sippy regimen virtually requires hospitalization and is an uncertain business at best, and I am inclined to believe that the general practitioner will do better to forego its use in the moderately severe case.

The severe or very severe case will require the most intensive form of therapy. The patient must be put to bed and complete *neutraliza-*

tion of the gastric juice obtained with aluminum hydroxide. In order to shorten the time of treatment it will be desirable to prescribe the aluminum hydroxide throughout the 24 hours if the patient is hospitalized, or if there is a nurse in attendance, otherwise the patient should be asked to take it throughout the day and until 11 or 12 o'clock at night.

Surgery will ultimately be indicated for those individuals in whom recurrences are frequent and for whom a recurrence is a serious matter because of the severity of the distress. It is difficult under medical management to make these patients comfortable during an active phase while they are carrying on their daily work, and as a result they are forced to give up their ordinary activities for a period of rest—a course that is impossible for a large group of the population. However, if surgery is contemplated, it should be of a radical sort. The simpler operations such as a Billroth I, gastro-enterostomy and small resections of the antrum are generally insufficient to prevent a recurrence. It is much better to remove as much of the stomach as possible, making a large anastomosis according to the method of Polya. This decreases, to a large degree, the volume of hydrochloric acid and the large stomach serves to dilute whatever hydrochloric acid is ultimately secreted. The operation has the further advantage of removing a large portion of the ulcer-bearing area. On the other hand, marginal ulcers can develop following these very radical procedures and some patients are bothered afterwards by a feeling of weakness and distress after meals which is associated in some way with the rapid entry of food into the small intestine. If there is a contraindication to surgery, one is forced to use medical treatment.

If medical treatment is employed in the severe case, *how long should the patient receive bed rest?* It seems unwise to allow a patient to become active and go back to work before his ulcer is healed. If the ulcer does not heal under the best possible conditions, it is unlikely that it will heal in less satisfactory circumstances. Hence, it is my rule to keep the patient in bed or in a semi-active state until the ulcer has healed as shown by (1) the absence of symptoms (2) disappearance of occult blood from the stools and (3) disappearance of a crater as judged by the x-ray.

ing of an ulcerous lesion Acting on this premise I have set 3 months as an arbitrary time for keeping the gastric contents completely neutralized The regimen is then modified until ultimately the patient is down to five meals a day and taking only as much aluminum hydroxide as is necessary to restrict the secretion of hydrochloric acid

### SUMMARY

The treatment of peptic ulcer is divided into those measures which affect the local condition of the stomach and duodenum and those which benefit or control the general health of the patient

Local treatment aims toward reducing surface trauma, decreasing spasm in and about the ulcer, and reducing or eliminating gastric acidity These objectives may be accomplished by bland diets, frequent feedings and the use of antacids, for patients with an uncomplicated ulcer Surgery is reserved for those patients who will not or cannot follow an adequate medical regimen

Treatment of the general health of the patient is based on relieving or overcoming those factors of nervous tension, infection and fatigue which are known to cause reactivation In addition to the local and general treatment, the patient should be educated regarding the nature of his disease and receive careful instructions concerning his general health, particularly on how to prevent nervous tension, infection and fatigue Finally, the treatment of peptic ulcer should not be standardized, but the type of local treatment should be decided by the severity of the disease in each particular individual

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# SUGGESTIONS FOR THE TREATMENT OF KIDNEY DISEASE

GEORGE W THORN, M D, F A C P \* and FRANK H TYLER, M D †

RENAL malfunction is characterized by excessive excretion or retention of normal constituents of the blood. Evidence of renal malfunction is usually manifested by the presence of protein, casts or cellular elements in the urine and by impaired performance of standardized tests of renal function. For purposes of discussion the principal causes of kidney disease may be grouped as follows:

1. Infections of the Kidney  
Pylonephritis, pyonephrosis, cortical abscesses and perinephric inflammation
2. Allergic Disorders of the Kidney  
Acute and chronic glomerulonephritis including the nephrotic syndrome, disseminated lupus erythematosus and polyarteritis
3. Disturbances in Renal Circulation  
Arteriole nephrosclerosis, heart failure, arterial and venous obstruction
4. Renal Injury from Chemical and Metabolic Agents  
Mercury, bismuth, sulfonamides and gout
5. Malformations (congenital or acquired) of the kidney  
Hypoplasia, polycystic disease, tumors and aberrant vessels

## GENERAL CONSIDERATIONS

**Infections of the Kidney**—The recognition of infections of the kidney and the institution of appropriate medical and surgical measures may prevent progressive and widespread destruction of kidney substance in many patients. The use of the sulfonamides, penicillin and mandelic acid represents a great advance in specific therapy.

**Acute Glomerulonephritis**—There is no specific therapy for patients with acute glomerulonephritis. Fortunately more than 85 per cent of patients suffering from this disease recover completely.<sup>1</sup> The number of recoveries may be increased appreciably by intelligent and diligent medical care. There is some evidence to suggest that patients who continue to have positive throat cultures for beta hemolytic streptococci are benefited by the use of sulfonamide therapy.<sup>2</sup>

**Disturbances in Renal Circulation**—In patients with renal insufficiency resulting from vascular disease there remains a great field for



TABLE 1—THERAPEUTIC MAN

TREATMENT		EDEMA			
		I Edema Hypoalbumin- emia	II Edema Hypoalbumin- emia Hypertension	III Edema Hypoalbumin- emia Hypertension Heart failure	IV Azotemia
<i>Total Fluids</i>		1500 cc. daily	1500 cc. daily	1000-1500 cc	4000 cc daily
<i>Diet</i>	Protein	2-3 gm /kg daily	1-2 gm /kg daily	milk daily for 2-5 days, no additional fluid or food	1 gm /kg daily
	NaCl	Salt free	Salt free		No restriction, 1-3 gm daily supplement <sup>‡</sup>
	Ash	Acid	Acid		Alkaline
<i>Diuretics</i>	Plasma or albumin*	25-50 gm. I V daily	10-15 gm. I V b.i d		
	Urea†	30-60 gm daily	30-60 gm daily	30 gm. daily	
	Glucose				1000 cc 5% I V daily 3-7 days
	Digitalis			Digitalization†	
	Aminophyl- line			0.1 gm. I V 0.1 d	
<i>Special Considerations</i>		In the presence of anemia whole blood transfusions are indicated.	In the presence of nausea and vomit- ing glucose solution 500 cc 10% I V q 6-8 hrs, albumin or plasma 8-10 gm I V q 6-8 hrs may be substitu- ted for above	Oxygen Paracentesis Fluids and protein solu- tions should not be given intravenously	In the presence of nausea and vomiting glu- cose solution 3000 cc. 10% I V, sodium chloride 500 cc 0.85% I V daily may be substituted for above.

\* The products of plasma fractionation employed in this work were developed from blood collected by the American Red Cross by the Department of Physical Chemistry, Harvard Medical School, Boston, Massachusetts, under a contract, recommended by the Committee on Medical Research between the Office of Scientific Research and Development and Harvard University. Albumin will not be available for general clinical use during the war because of the needs of the armed forces.

† Urea may be given in fruit juice. If anorexia or nausea occurs, the dose of urea should be reduced or discontinued.

## AGEMENT OF KIDNEY DISEASE

AZOTEMIA		EDEMA AND AZOTEMIA		
V Azotemia Acidosis	VI Azotemia Acidosis Hypertension	VII Edema Azotemia Acidosis Hypertension	VIII Edema Hypoalbumin emia Azotemia Hypertension	IX Edema Azotemia Acidosis Heart Failure
4000 cc. daily	3000 cc. daily	2000 cc. daily	2000 cc. daily	1000 cc milk daily with aluminum hydroxide ad- ded <sup>1</sup> , 500-1000 cc. fruit juice
1 gm./kg. daily	1 gm./kg daily	1 gm./kg daily	1 gm./kg daily	
No restriction, 1-3 gm daily supplement <sup>2</sup>	No restriction	Salt free	Salt free	
Alkaline 3-6 gm. NaHCO <sub>3</sub> daily	Alkaline 3-6 gm. NaHCO <sub>3</sub> daily	Alkaline	Alkaline	
		10 gm. IV b.i.d.	15 gm. IV b.i.d.	
1000 cc. 5% LV daily 3-7 days	50 cc. 20% LV daily 3-7 days			See footnote <sup>3</sup>
				Digitalization <sup>4</sup>
		0.1 gm. IV b.i.d.	0.1 gm LV b.i.d.	0.1 gm LV b.i.d.
The contents of one 40 cc. am- pule of sodium lactate (11%) may be added to the above solution daily for 3-4 days in place of sodi- um lactate by the	In the presence of nausea and vomiting glu- cose solution 10% IV slow- ly not to ex- ceed 1000 cc. q 8 hrs 500 cc. 0.5% NaCl q 3rd day in ab- sence of ede- ma may be substituted for above		In the presence of nausea and vomiting glu- cose solution 750 cc. 10% IV q 8 hrs. albumin or plasma 8 gm. IV q 8 hrs. may be sub- stituted for above	Oxygen. Paracentesis. Venesection in presence of high venous pressure. Fluids and pro- tein solutions should not be given intrave- nously.

<sup>1</sup> In the absence of previous dialysis therapy 3 cat units intramuscularly, and 2 cat units orally may be given.  
<sup>2</sup> The so-called sodium chloride tablets (1 gm each)  
<sup>3</sup> 10-15 cc of aluminum hydroxide may be added to each glass of milk  
<sup>4</sup> 10-15 cc of aluminum hydroxide may be added to each glass of milk  
<sup>5</sup> 10-15 cc of aluminum hydroxide may be added to each glass of milk  
<sup>6</sup> 10-15 cc of aluminum hydroxide may be added to each glass of milk

therapeutic progress At present therapy is limited to the treatment of congestive heart failure and attempts to lower blood pressure by medical and surgical methods

**Renal Insufficiency from Chemical and Metabolic Agents.**—The widespread use of chemotherapeutic agents undoubtedly will increase the occurrence of renal disease Here the problem is largely one of prophylaxis, since the incidence of renal insufficiency can be greatly reduced if precautions are taken to ensure an adequate urine volume

**Malformations of the Kidney**—In hypoplasia and cystic disease of the kidney little can be done other than to prevent secondary infection In the presence of renal stasis resulting from calculus, an aberrant vessel or tumor, surgery may be effective in improving kidney function or in preventing further damage

It is apparent from these considerations that the elimination of the agent responsible for renal damage is not possible in most patients with kidney disease Hence treatment must be concerned largely with the application of measures designed to preserve nephrons and prevent development of gross chemical and metabolic abnormalities It is not generally appreciated that a useful life including moderate activity may be carried on for many years despite the reduced functioning kidney mass This is particularly true of patients with renal insufficiency without hypertension

## THERAPEUTIC CONSIDERATIONS

### I. Water Requirement

#### Principles

- A In the absence of circulatory failure water will not be retained in the body in significant quantity without the concomitant retention of *sodium*, hence in patients with "renal" edema there is little justification for the restriction of fluids on a salt-free regimen
- B A large urine volume is advantageous in the presence of azotemia

In patients with *edema* without azotemia (nephrotic syndrome) a daily fluid intake of 1500 cc is usually adequate (Table 1 Types I and II) The quantity of fluid may be reduced if the patient so desires In the presence of *azotemia* without edema (chronic glomerulonephritis, arteriolar nephrosclerosis, chronic pyelonephritis) it is distinctly advantageous to increase the 24-hour urine volume to 2000–3000 cc This usually requires the administration of approximately 4000 cc of fluid daily (Table 1 Types IV, V and VI) Under these circumstances, however, essential as well as nonessential substances may be "washed out," hence the need for replenishing the former In patients with *azotemia* and *edema* it is obvious that some compromise in fluid intake is necessary, thus in the absence of cardiac failure 2000 cc fluid intake is suggested (Table 1 Types VII and VIII)

In the presence of infections of the kidney a large output of urine is to be desired. When the volume of urine is increased in the treatment of pyuria the dose of chemotherapeutic substance may need to be increased to provide an adequate concentration of bacteriostatic agent in the urine.

Edema and dehydration are frequent complications of renal malfunction, hence the necessity for a study of "water balance" frequently arises. Unfortunately, to most physicians the term "water balance" implies only measurement of fluid intake and urine output.

TABLE 2—DETERMINATION OF WATER BALANCE

<i>Intake</i>		
1 Liquids		
Measure fluid intake directly		
2 Water content of solid food		
Calculate by weighing aliquot of day's diet before and after drying or by consulting tables for average water content of foods.		
3. Water of oxidation		
1 gm. protein = 0.4 gm. water		
1 gm. carbohydrate = 0.6 gm. water		
1 gm. fat = 1.0 gm. water		
<i>Output</i>		
1 Urine		
Measure urine volume.		
2. Feces		
Determine wet and dry weight of feces.		
3. Insensible water loss and perspiration		
Weigh patient at 9:00 p. m. and again at 9:00 a. m. under standard conditions without food or fluid intake in the interim.		
4. Abnormal water losses		
Saliva, sputum, draining fistulae, etc. measure directly		
<i>Example</i>		
Diet: Carbohydrate 270 gm., protein 70 gm., fat 120 gm.		
Fluid intake.	1500 cc.	
Water content of food	600 cc.	
Water of oxidation	240 cc.	2340 cc.
Urine volume	1200 cc.	
Water content of feces	250 cc.	
Insensible water loss and perspiration ( $465 \times 2$ )	930 cc.	
Abnormal loss.	0 cc.	2340 cc.

presence of oliguria, a most helpful method of detecting dehydration in most circumstances, cannot be relied upon in patients with nephritis

Parenteral administration of fluids and nutritive substances must be employed in patients with renal insufficiency who are unable to retain fluids and food by mouth. Fluid absorption by rectum is rarely sufficient to meet daily body requirements. The absorption of nutritive substances from the rectum is unpredictable.

In the presence of nausea and vomiting it may be stated that the minimum body requirements are as follows

Water	2500 cc daily
Calories	1200 daily
Protein	25-50 gm daily

For parenteral fluid administration one is limited to the use of solutions of glucose, saline, protein or amino acids. Since in most instances protein administered parenterally will supply less than 200 calories per day (i.e., 25-50 gm  $\times$  4 calories per gm) it is apparent that most of the caloric requirement must of necessity be derived from glucose solutions. Two hundred and fifty grams of glucose is needed to provide 1000 calories (250 gm  $\times$  4 calories per gm), and therefore the administration of 2500 cc of 10 per cent glucose daily will provide both fluid and minimum caloric requirement. Continued use of parenteral glucose solutions, however, may result in a striking fall in the serum level of sodium and chloride, and the possible need for supplementary sodium chloride therapy during periods of active diuresis induced by glucose solutions must always be kept in mind (Table 1 Types IV, V and VI)

## II Dietary Management

### Principles

Patients with nephritis should be provided with basic dietary requirement necessary for health. Water sufficient to provide a urine volume large enough to permit excretion of end-products of metabolism, calories sufficient to maintain weight, protein sufficient to meet the body needs (1 gm per kg per day for adults) and to compensate for abnormal losses in the urine, essential minerals and vitamins.

**Protein Content of Diet**—Patients with disease of the kidneys frequently are deficient in protein. In the absence of azotemia high-protein diets are indicated, i.e., 2 to 3 gm of protein per kilogram of body weight per day. High-protein intake is of advantage in the treatment of patients with edema without azotemia for the following reasons: (1) improved nitrogen balance, (2) increased urea excretion (diuretic), (3) increased renal blood flow and (4) acid ash (diuretic).

In the presence of azotemia protein intake may be restricted to the basic requirement of 1 gm per kilogram of body weight per day. Plasma and albumin solutions recommended in the treatment of edema are useful sources of protein, but their prime function when given intravenously in quantities now available is their *diuretic action*. Patients who are nauseated and who are unable to retain food for more than 2 or 3 days may be given amino acid solution, plasma, albumin or blood parenterally at regular intervals as a source of required dietary protein. It should be borne in mind that it is practically impossible to induce a positive nitrogen balance by parenteral protein or amino acid therapy alone!

TABLE 3—APPROXIMATE CALCULATIONS FOR ACID-BASE CONTENT OF DIET\*

	Grams	Household Measure	Excess Acid†	Excess Base‡
Vegetables§	100	½ cup		6.2
Fruit§	100			5.1
Meat, fish, poultry	100	3½ oz.	10.5	
Eggs	100	2	11.0	
Cereal¶	180	½ cup	3.2	
Bread	30	1 slice	2.0	
Milk	120	½ cup		2.1
Milk	180	¾ cup		3.2
Milk	240	1 cup		4.3
Cheese	20	1" cube	1.1	
Potato	100	½ cup		7.0
Macaroni, noodles, rice and spaghetti§	150	½ cup	3.1	
Cornstarch or tapioca pudding..	100	½ cup		1.5
Rice pudding	100			1.3
Baked custard		½ cup	0.1	
Pastry cake	60		2.5	

\* Chazy, Margaret S., and Ahlborn, Margaret. Nutrition. Boston, Houghton Mifflin Company, 1937, pp. 386-409.

† Expressed as cc. normal solution required to neutralize the ash.

‡ Cheese does not include spinach and dandelion greens (excess base 27.0) or corn (excess acid 1.8).

§ Vegetable does not include prunes, plums and cranberries which are excess acid foods.

|| Oysters does not include oysters (excess acid 15.2).

¶ Calculated weight.

sodium chloride, 2 to 3 gm of sodium chloride and 5 to 6 gm of sodium bicarbonate (sodium content of sodium bicarbonate is approximately one-half that of sodium chloride) may be given. In chronic renal insufficiency with a large fluid intake and output it is possible to "wash out" excessive quantities of sodium and chloride with disastrous results, hence the need of replacement therapy.

**Ash of the Diet**—In the presence of edema without azotemia or acidosis (nephrotic syndrome) (Table 1 Types I and II) an acid-ash diet may be of some aid in promoting diuresis. Furthermore, since the ideal diet for such patients is one containing a large quantity of protein, the ash will most certainly be acid. A problem is presented in the treatment of patients with azotemia and acidosis (Table 1 Types V, VI and VII). In this situation the kidneys are unable to conserve base, since the ability to form ammonia from urea is greatly reduced. Sodium and other fixed bases are drawn from the body and excreted to assist in neutralizing acid end-products. Decreasing the acid ash residue of the diet by ingesting a diet of neutral or alkaline-ash composition may be helpful (Table 3). Aluminum hydroxide may also be added to milk or taken with food. By so doing a great reduction in phosphorus (fixed acid) absorption can be demonstrated and the relative alkalinity of milk can be greatly increased.<sup>3</sup> Supplementary sodium bicarbonate therapy may be given to patients with renal acidosis without edema. The water retaining effect of sodium bicarbonate is equivalent to approximately one-half to one-third that of sodium chloride, i.e., 2 to 3 gm of sodium bicarbonate is equivalent to 1 gm of sodium chloride. In patients without edema with renal acidosis, nausea and vomiting, sodium lactate or sodium bicarbonate may be given intravenously. One 50-cc ampule of sodium lactate (11 per cent) may be added to the glucose solution and given once or twice a day until a satisfactory increase in carbon dioxide combining power has been attained (Table 1 Type V).

### III Diuretics

#### Principles

There are two indications for increasing urine output in patients with renal malfunction, (1) edema and (2) azotemia. In patients with kidney disease one can scarcely justify the use of diuretics which depend for their action on an irritative or toxic effect on the renal tubules. It would appear more rational to employ agents which act by increasing plasma volume and renal circulation, i.e., protein solutions intravenously, glucose solutions intravenously, urea and possibly xanthine derivatives. The presence of circulatory failure, however, is a contraindication to the use of substances which depend for their action on a relatively large increase in plasma volume.

**Edema.**—Edema is usually related to hypoalbuminemia and is most commonly observed in the nephrotic syndrome (Table 1 Types I and II) Salt restriction is indicated under these circumstances Administration of urea may be quite effective in many cases (Fig 93) It may require 10 to 20 days of urea therapy (30 to 60 gm. daily) before the diuretic action of this substance is manifested Fluid intake should be limited to 1000 to 1500 cc daily during the period of urea administration, and blood nonprotein nitrogen determinations should be made at 5 to 7 day intervals. Little effect of urea as a diuretic can be expected unless the administration of urea results in an elevation of blood urea nitrogen It is obvious, however, that the mechanism re-

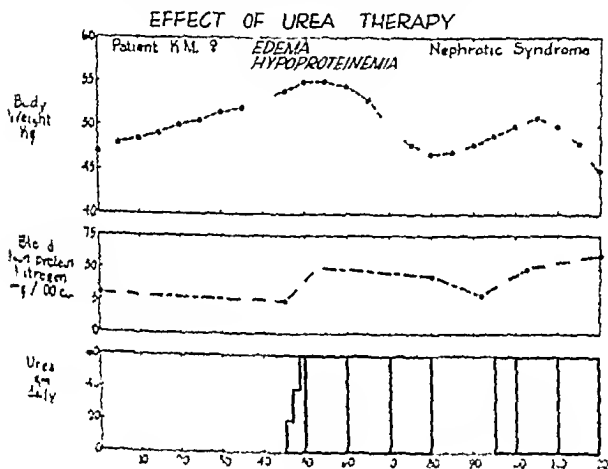


Fig 93



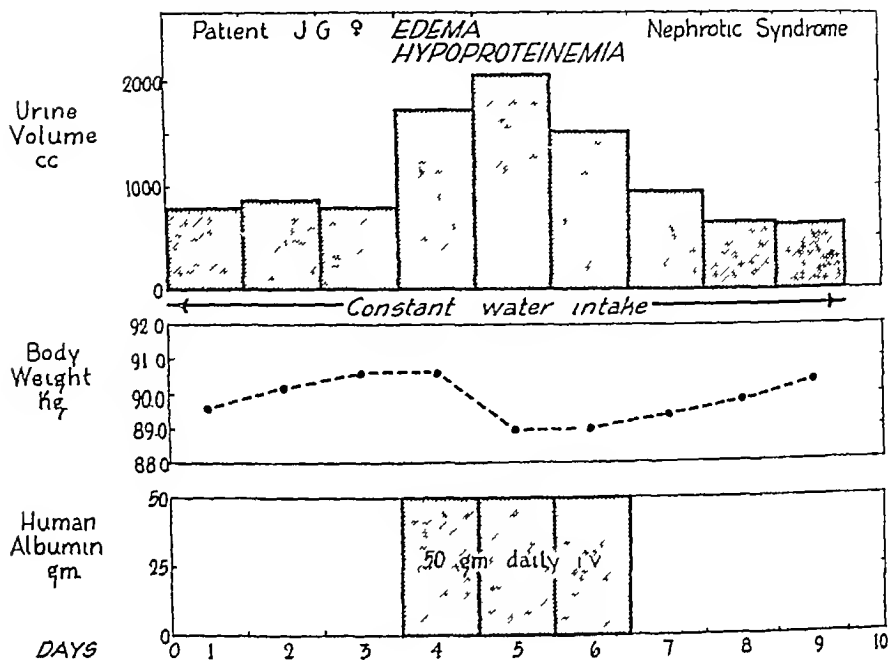
EFFECT OF INTRAVENOUS ALBUMIN  
ON URINE OUTPUT

Fig 94

## Patient B B Nephrotic Syndrome

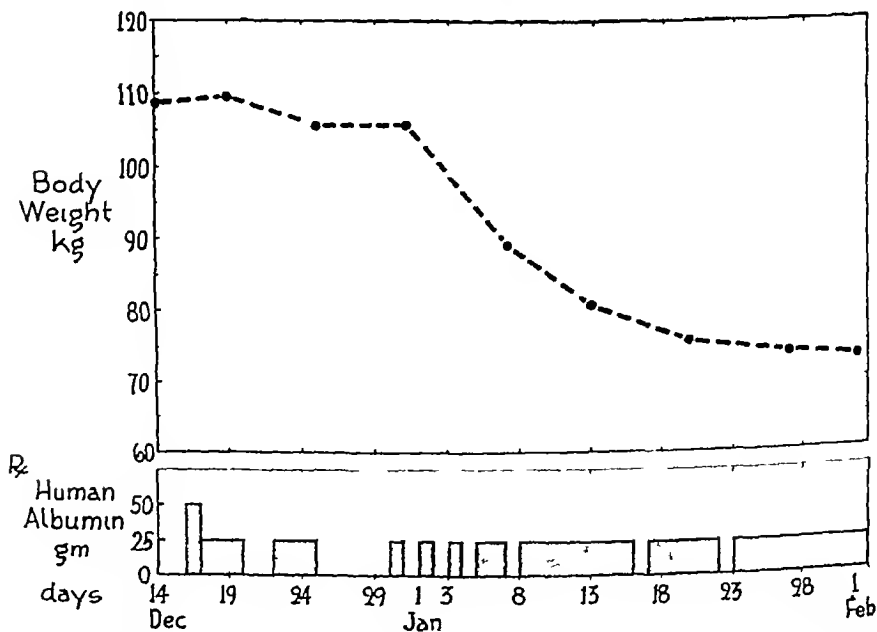


Fig 95—Changes in body weight and edema following the long-continued intravenous administration of human albumin in nephrotic syndrome (From Thorn, G W., New England J Med., 1943)

exert as potent a colloid osmotic effect as 1 gm. of albumin. As a diuretic agent for patients with edema it is extremely important to point out that human albumin can be prepared with a low sodium chloride content. In the treatment of edema such a preparation would have a great advantage over plasma solutions which contain rather appreciable quantities of sodium chloride (Table 1 Types I and II).

**Azotemia**—Patients with azotemia without significant hypoalbuminemia will usually have a diuresis following the administration of large quantities of fluid by mouth (Table 1 Types IV, V and VI). In marked azotemia, however, it is many times helpful to give 3 to 7 days' treatment of 1000 cc. of 5 per cent glucose intravenously in conjunction with a large fluid intake. In the absence of edema it is desirable to give some supplementary sodium chloride during this period of therapy, e.g., 1 to 3 gm. daily.

In acute nephritis with striking edema and azotemia there is usually moderate reduction in serum albumin level<sup>4</sup> and an increase in blood nonprotein nitrogen. It is obvious that the reduction in colloid osmotic pressure is not sufficient to explain the edema in most patients. Protein solutions administered intravenously to patients with acute nephritis do not have as striking a diuretic effect as in patients with the nephrotic syndrome and marked hypoalbuminemia. Furthermore, great care must be exercised in the administration of protein solutions to patients with acute nephritis and edema in order to prevent cardiac dilatation following a sudden increase in plasma volume. Fluids by mouth or intravenously are not as effective in reducing azotemia as is the case in azotemia due to chronic nephritis. The treatment of oliguria and azotemia in patients with acute nephritis with nausea and vomiting requires considerable skill and judgment in the use of small quantities of protein solution intravenously in conjunction with glucose solution. Serum chloride levels and carbon dioxide combining power must be followed carefully, as occasionally a striking degree of hypochloremia may develop even in the presence of edema (Table 1 Type VIII).

#### TREATMENT OF PYELONEPHRITIS INCLUDING PYELITIS

icated particularly in patients with infections of the kidney with renal insufficiency The possibility of renal damage from sulfonamide therapy must be kept in mind

### *Illustration*

Patient N S, P.B.B.H Med No 66,182, male, aged 68

*Diagnosis* Bilateral pyelonephritis (*E coli*)

*Complication* Diabetes mellitus

*Examination* Blood pressure was 140/70 mm of mercury, temperature ranged between 98.6° and 101° F, white blood count was 13,000 with 65 to 80 per cent polymorphonuclears, blood urea nitrogen was 9 mg per 100 cc. There was no evidence of significant impairment in renal function The urine was observed to contain sugar 1 to 2+, protein 1 to 2+, clumps of pus cells and white blood cells, no casts, an occasional red cell, specific gravity 1.010-1.018

*Treatment* Fluids 2500 to 3500 cc daily, sulfadiazine 1 gm three times a day Four days after therapy was instituted pus cells and white blood cells in the urine were reduced to 0 to 2 per high-power field There were no casts, no red cells Protein was 0, sugar± These findings remained constant during the next 8 days The treatment was discontinued at the end of a total of 12 days The patient was then discharged from the hospital

*Recurrence* of urinary tract infections in such patients occurs frequently There is still considerable debate as to the therapeutic management of such cases after the initial infection has cleared Two courses are open

1 Continued administration of small doses of sulfadiazine as a prophylactic measure

2 Withdrawal of treatment after evidence of acute infection has subsided, with the administration of a therapeutic agent with recurrence of infection

The strongest argument against continued administration of small doses of a sulfonamide as a prophylactic measure is the possibility of developing a strain of "drug-fast" organisms

In urinary tract infections which are resistant to sulfonamide therapy or as an alternate method of therapy, *mandelic acid treatment*<sup>5</sup> should be considered This form of therapy is not effective against certain genera of proteus, *Bacillus pyocyaneus* and other urea-splitting organisms, since the ammonia so formed from urea breakdown as the result of bacterial action prevents the urine from becoming sufficiently acid to permit the bacteriostatic action of mandelic acid Calcium mandelate or mandelic acid should be given in quantities sufficient to attain a concentration of 0.5 to 1.0 per cent in the urine The hydrogen ion concentration of the urine should be maintained below 5.5 (red to methyl red indicator) *Example* In the presence of a urine volume of 1000 cc daily 10 gm of calcium mandelate must be given daily to attain a concentration of 1 per cent in the urine In most instances fluid intake is restricted to approximately 1500 cc daily Calcium mandelate tablets are given in a dose of 3 gm four times a day (a total daily dose of 12 gm) Treatment should be continued for 10

to 12 days and then discontinued. Treatment should not be reinstituted before the expiration of a 2 weeks' interval.

*Note* Patients with renal insufficiency (azotemia) should not be treated with acid salts (ammonium chloride and mandelic acid).

#### TREATMENT OF TUBERCULOSIS OF THE KIDNEY

Nephrectomy is desirable in patients with unilateral active renal tuberculosis. Under these conditions it is important that such patients receive the equivalent of sanatorium care prior to and following operation. The possibility of latent adrenal insufficiency should be considered in all patients with urogenital tuberculosis.<sup>6</sup> *Adrenal cortical hormone therapy* should be available during and following operation.

#### TREATMENT OF ACUTE GLOMERULONEPHRITIS

Patients with acute glomerulonephritis who continue to have positive throat cultures for beta hemolytic streptococci may be benefited by the use of sulfonamide therapy.<sup>2</sup> Because of the possibility of renal complications which might arise from sulfonamide therapy the use of *penicillin* in such patients should be seriously considered.

#### Illustration

Patient M. K., P.B.B.H. Med. No. 65,806, male, aged 21.

*Diagnosis* Mild glomerulonephritis with persistent positive throat culture for beta hemolytic streptococcus.

*Present Illness* Eight days prior to entry the patient had a severe sore throat. Beta hemolytic streptococci were cultured from the throat. Five days before entry the sore throat had markedly cleared but the patient had general malaise. Three days before admission the patient noted pain in his back.

*Examination* On admission blood pressure was 130/85 mm. of mercury, temperature 99.6° F and pulse rate 96. There was slight generalized edema. The throat was injected and the heart slightly enlarged. Urinalysis revealed 1+ protein, 1 to 75 red blood cells per high power field, 2 to 10 white blood cells per high power field and an occasional granular cast.

*Treatment* Because beta hemolytic streptococci persisted in cultures of the throat sulfadiazine was given 6 gm. daily for 5 days and then 3 gm. daily. Three to 6 gm. daily of sodium bicarbonate was administered in conjunction with this. On the eleventh hospital day the urine was free of protein and formed elements. The patient was discharged from the hospital on the twenty-fourth hospital day.

## TREATMENT OF THE NEPHROTIC SYNDROME

Suggestions for the treatment of patients with the nephrotic syndrome are outlined in Table 1 Types I, II and III The use of *plasma* or *albumin* solutions for their diuretic effect is illustrated in Figs 94 and 95 The possible value of continued administration of parenteral protein solutions over long periods of time is illustrated in the treatment of patient B B (Fig 95) Unfortunately, at the present time the supply of albumin available for civilian use is very limited It should be pointed out that there is no doubt that human albumin given intravenously to patients with the nephrotic syndrome is an excellent physiological diuretic agent especially if a preparation of human albumin low in sodium chloride is employed There is no proof to date, however, that the continued administration of albumin intravenously has any effect on the course of the disease<sup>7</sup>

One of the safest and most effective diuretics for use in patients with the nephrotic syndrome without edema is *urea* The effectiveness of treatment with this agent is illustrated in Fig 93 When urea is not well tolerated it is best discontinued, since the induction of nausea and vomiting coincidental with its administration offsets greatly the value of urea therapy by reducing the dietary protein intake

It is difficult for many patients with the nephrotic syndrome to ingest a diet of high-protein content (2 to 3 gm per kg of body weight) Under these circumstances supplementary *amino acid solution* by mouth may provide a very effective means of maintaining nitrogen balance Twenty to 60 gm of amino acid may be taken daily by most patients with little discomfort

## TREATMENT OF RENAL INSUFFICIENCY ASSOCIATED WITH CHRONIC GLOMERULONEPHRITIS, CHRONIC PYELONEPHRITIS AND ARTERIOLAR NEPHROSCLEROSIS

The majority of patients with these disorders exhibit high-grade renal insufficiency and azotemia In the absence of active infection and in the absence of indications for surgical intervention, therapy is indicated largely by the physiological needs required to correct the underlying chemical and metabolic disturbances Suggestions for the treatment of patients with high-grade renal insufficiency are summarized in Table 1 Types IV, V, VI and VII Patients with azotemia without hypertension may be rehabilitated for periods of months to years despite high-grade renal insufficiency (Table 1 Types IV and V)

*Illustration*

Patient J T., P.B.BH Med No 63,653, male, aged 53

*Diagnosis* Pyelonephritis with azotemia and acidosis

*Examination* There was considerable cardiac enlargement without edema or anemia with high-grade azotemia and moderate acidosis Blood pressure ranged from 165/100 to 185/110 mm of mercury Urinalysis revealed a maximum concentration of 1 012, protein 1+, many red blood cells and leukocytes in the sediment.

**Treatment** The patient was given a fluid intake of 3000 to 4000 cc. per day and 1 gm. of protein per kg. of body weight. Sodium chloride content of the diet was not restricted. The diet, however, was alkaline ash, and aluminum hydroxide (8 cc.) was added to each glass of milk. In addition a daily injection of 50 cc. of 20 per cent glucose was given intravenously for 7 days. On this regimen the blood urea nitrogen fell from 78 to a level of 27 mg. per 100 cc. The serum carbon dioxide combining power increased from 10.2 to 23.4 millimols per liter. On this regimen the patient was able to return to work. Because of a gradual reduction in serum chloride level the patient was given 2 to 3 gm. of added sodium chloride and 3 gm. of sodium bicarbonate. Increasing the dose of sodium chloride or bicarbonate above this quantity resulted in edema formation. Reducing the sodium chloride below this level resulted in an increase in azotemia.

### SUMMARY AND CONCLUSIONS

In the absence of active infection and in the absence of indications for surgical intervention, therapy for patients with renal malfunction is dictated largely by the physiological needs required to correct the underlying chemical and metabolic disturbances. The disorders which commonly attend renal malfunction are as follows

Edema and hypoalbuminemia

Anemia

Anorexia, nausea and vomiting

Azotemia and acidosis

Hypertension and heart failure

In the care and treatment of patients with kidney disease one should have available facilities for determining blood urea nitrogen or non-protein nitrogen, total serum protein concentration, serum chloride and carbon dioxide combining power. It is also desirable from time to time to obtain accurate measurement of heart size with teleroentgenograms. Practically all that can be accomplished in correcting the metabolic disturbances associated with renal malfunction can be accomplished by the judicious use of relatively simple agents, i.e.

Water

Minerals— $\text{NaCl}$ ,  $\text{NaHCO}_3$ ,  $\text{N}_2$  lactate and  $\text{Al}(\text{OH})_3$

Urea

Glucose solutions

Solutions containing protein—plasma, albumin and whole blood

A diet containing the basic nutritional requirements for health

Fundamental considerations in the treatment of patients with kidney disease have been presented and an outline of therapy has been suggested. No attempt has been made to suggest forms of therapy for the conditions which result in renal malfunction.

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# CHRONIC DIARRHEA AND ITS TREATMENT IN INFANCY AND CHILDHOOD

LOUIS K. DIAMOND, M.D.\*

THE proper care and treatment of children with chronic or recurrent diarrhea have been hampered by many concepts that have been handed down from earliest times, if not in actual medical teaching, certainly by word of mouth from layman to layman.

Such misconceptions start with the belief that all infants and small children normally should have frequent loose movements even while entirely well, and that constipation of the mildest type, such as is suggested by the evacuation of one firm smallish movement per day, is unnatural and may cause a variety of symptoms, from mere unhappiness or poor appetite to severe irritability and loss of weight, or even to generalized convulsions. In recent times, advertising agencies, using the radio and lay press, have stressed the desirability of a "full" and "regular" evacuation to dissipate many subjective symptoms.

The next frequently encountered impression is that diarrhea is natural in "teething" children and may suddenly become more severe when a tooth is being "cut." Since this normal phenomenon of teething is frequent, if not constant, from the sixth to the thirtieth month of life it can always serve as an easily demonstrable excuse for the onset of diarrhea.

Finally, if other ready causes are desired, the diet is always subject to criticism, for a new food or a larger quantity of an everyday food is likely to have been ingested in the preceding interval from an hour to a week before the stools became frequent and loose.

That these causes for diarrhea have been accepted for generations is evidenced by a brief excursion into older medical writings, often expressed in more vivid language than is now employed. For example, in one of the earliest pediatric discussions, by a French physician Mauriceau in 1727 a chapter entitled "Of the Looseness of an Infant" states: "As soon as little infants are in the least indisposed they very ordinarily get a looseness to which their natural moistness very much contributes. For the most part, the loosenesses happen to them by reason of the great pain they have at the cutting of their  
teeth."



to remedy it, lest the child, composed of a tender and soft substance (easy upon this account, if one may so say, to be melted) be not too much enfeebled by it, because of the great dissipation of spirits, which the continual evacuation of humours flowing through the belly effects" Therefore, "ever respect above all the cause of the looseness and the accidents complicated with it"

Underwood, one of the earliest authors of a pediatric text (1814), discussed the commonness of diarrhea in children and, after suggesting various sorts of remedies, warned that "purging," meaning diarrhea, is not a disease and that the cause of it must be removed while the ill effects must be guarded against by keeping it (the "purging") within bounds

The idea that diarrhea is a symptom and not a disease is therefore exceedingly old, and the logical first step in rational treatment of the complaint is to seek the underlying cause. In the differential diagnosis of chronic diarrhea in infancy and childhood, we now investigate the following etiologic possibilities. The order of consideration, namely (1) infection, (2) congenital malformation, (3) pancreatic fibrosis, (4) allergy and (5) celiac disease, is purposeful and logical, as will be pointed out later. Each of these will now be reviewed in greater detail with particular emphasis on procedures for diagnosis and methods of treatment.

### INFECTION

Probably the most common cause for chronic and recurrent, as well as acute, diarrhea in infancy and early childhood is infection. Although it is commonly accepted that infection within the intestinal tract, i.e., enteric infection, will usually cause diarrhea of varying severity, it is not always appreciated that infection outside the intestinal tract, i.e., parenteral infection, may be the basis for diarrhea. In fact, the greater prevalence of parenteral infection makes this more often so, and the younger the child the more commonly parenteral infection causes diarrhea.

In the enteric infections, the *typhoid-dysentery* group of organisms are the most serious. While they usually tend to cause acute symptoms, they may occasionally be the causative organisms in a more chronic or recurrent diarrhea. This is more likely with the less virulent salmonella group. An important aspect of the need for early diagnosis here is the public health consideration—the danger of spread of the infection in the family, in the community and especially in the hospital, if the patient is not properly isolated and the excreta properly disposed of.

*Tuberculosis* is a relatively uncommon basis for enteritis in childhood, but it should be seriously considered as a cause for chronic diarrhea, particularly if there are evidences of tuberculosis elsewhere in the body.

*Intestinal parasites*, in the past, have played a relatively minor role in the etiology of chronic diarrhea in children in this country. The most important parasite in this group has been the *Endamoeba histolytica* which has caused not only sporadic but also epidemic outbreaks of severe diarrheal disease. Heavy infestation with *Giardia lamblia* is reported to have caused serious intestinal disturbances in children. After the present world conflict these and probably other parasites may increase in importance as causes for chronic diarrhea, as the result of the return to this country of men who have contracted intestinal parasitic diseases in the tropics and become carriers of the parasites.

Two other morbid processes within the bowel, often associated with chronic diarrhea, are *ulcerative colitis* and *regional ileitis*. From time to time, various pathogenic organisms have been blamed for the pathologic state in each of these conditions but no uniformity of opinion exists in this regard.

As stated above, parenteral infection is the most frequent cause of chronic or recurrent diarrhea, and the younger the patient the greater the number of instances in which this is found. In the severely debilitated infant with diarrhea, parenteral infection is often present and it may be difficult to establish whether it antedated the intestinal complaint or was a secondary invader as nutrition failed. Almost any site of infection may precipitate diarrhea. Nasopharyngitis, sinusitis, otitis and mastoiditis are the commonest causes. Lower respiratory tract infections are also frequent. Pyelonephritis and other infections of the genito-urinary tract are probably next in order of importance. Almost any system of the body which harbors infection may be responsible for a long standing diarrhea. And most important, while the infection persists, the increased number and bulk of the bowel movements may continue.

enlarged spleen, so common in enteric infection, or of a large or tender kidney mass from infection in this area, are important findings.

In *laboratory procedures*, the first step should consist of the gross examination of the stool. The presence of blood or pus demands the use of proper precautions against possible spread of a pathogenic organism from the patient to the contacts. Cultures of freshly-passed feces should be repeated until a sufficient number of negative results have been obtained (three or more) to offer assurance that the stools do not contain the common pathogens. Should these be demonstrably absent, examination of fresh material for tubercle bacilli (especially if the child shows a positive tuberculin test), or for amebae or other parasites must be carried out by suitable technic.

The urine requires careful and repeated examination to exclude the presence of pus cells as evidence for cystitis, ureteritis, pyelitis and pyelonephritis. Should there be pyuria or any other suggestion of infection in the genito-urinary tract, culture of the urine is indicated to identify the causative organism.

The determination of the leukocyte level and a differential count of the white blood cells is indicated in this as in any question of infection.

Agglutination tests using the patient's serum and the common enteric organisms are helpful. A positive result with a specific bacterium, if the patient has not been prophylactically treated with a specific vaccine in the past, may establish the diagnosis of typhoid, paratyphoid or salmonella infection.

Cultures of exudates from the middle ears or the nasopharynx, or of the material obtained by swabbing the posterior pharynx or the tonsils, are indicated if infection in the respiratory tract is suspected. Should these yield large numbers of pathogenic organisms, either singly or in mixture, specific therapy may be applicable.

Finally, *roentgenograms* of the sinuses, mastoids and chest, if infection of the upper respiratory passages is likely or has been suggested by the history, may offer a clue as to hidden foci of infection which may underlie the diarrhea and are causing it.

**Treatment**—In the care of the child with chronic diarrhea, it is of importance to relieve or eradicate foci of infection whether they be primary or superimposed on the diarrheal state. When the infection has brought about the diarrhea it may be well nigh impossible to improve this state until all foci have been completely removed. Even with so specific a mode of therapy as the use of liver extract in pernicious anemia, it has been found that the presence of infection interferes with the beneficial effect of the treatment. Where no such specific therapy exists, as in the treatment of diarrheal disease, any remedial measures may be futile as long as infection persists.

In the treatment of the enteric infection, organisms of the typhoid-dysentery group may be difficult to eradicate from the intestinal tract when they have persisted there for a considerable time. Recent trials

Height, cm.	Ideal Body Weight, kg.	Basal Heat Production, Calories per day <sup>25</sup>
73	10	
115	20	550
137	30	870
150	40	1100
160	50	1250
170	60	1400
		1550

Provided the mineral, nitrogen and vitamin requirements are met patients suffer no damage from such underfeeding so long as excess body fat remains.

Sample diets\* follow:

1. 750 cal., P 53 gm., F 20 gm., CHO 90 gm.

*Breakfast*

- a. Orange juice,  $\frac{1}{2}$  cup.
- b. Toast,  $\frac{1}{2}$  slice, or cereal,  $\frac{1}{2}$  cup.
- c. Butter or oleomargarine,  $\frac{1}{2}$  square.

*Noon*

- a. Clear soup (broth, bouillon or consomme) ad lib.
- b. One egg or lean meat, fish, fowl or cottage cheese, 2 oz. or 5 tablespoons or a piece about  $\frac{1}{2} \times 2 \times 3$  inches.
- c. Vegetables, 2 servings ( $\frac{1}{2}$  cup each) raw or cooked without sauces.
- d. Fruit,  $\frac{1}{2}$  cup or equivalent.
- e. Skim milk,  $\frac{1}{2}$  cup.

*Night*

Same as at noon, but add  $\frac{1}{2}$  slice bread and  $\frac{1}{2}$  square butter.

2. 1000 cal., P 68 gm., F 30 gm., CHO 115 gm.  
Add to regimen 1, 1 cup skim milk, 1 slice bread, 1 egg,  $\frac{1}{2}$  square butter.
3. 1200 cal., P 70 gm., F 51 gm., CHO 115 gm.  
Substitute  $2\frac{1}{2}$  cups whole milk for the skim milk of regimen 2.

The following suggestions as to the choice of foods may be helpful. *Vegetables:* A serving of potatoes, kidney, lima, navy or soup beans and of corn shall be considered as  $\frac{1}{4}$  instead of  $\frac{1}{2}$  cup. Lettuce and celery may be used ad lib. All other vegetables equal  $\frac{1}{2}$  cup. *Fruits:* No sweetened fruit is to be used. Unsweetened canned fruits can be purchased. A serving of banana is  $\frac{1}{2}$  a small banana. *Meats, etc.:* All visible fat is removed. Ham, pork, bacon, wieners and picnic meats not allowed. Obviously fat fish, such as those packed in oil and such as mackerel, shall not be used. All cheese except cottage cheese is prohibited. *Method of Preparation:* Cook all foods without fat unless that allowed for the meal is used. Broiling, steaming or boiling is the method of choice for cooking meats. No flour gravies or sauces are allowed. At least one vegetable a day should be served raw. *Other Foods:* Prohibited!

**Other Therapy.**—Benzedrine sulfate (amphetamine sulfate) may be helpful in controlling the appetite. It should be given one-half hour before meals. The recommended adult dose for chronic medication is usually 10 mg. repeated three or four times daily. An appropriate fraction of this dose may be given to children. Since occasional patients

\* We are indebted to Miss S. Wells, dietitian in charge at the Metabolic Ward of the Massachusetts General Hospital, for these diets.

one or two soft to loose movements daily. In the ensuing 6 months there had been several periods of low-grade feverishness and visible redness of the tonsils and pharynx with some postnasal drip and frequent cough, especially at night. With each of these periods there had been a re-exacerbation of the diarrhea, the stools becoming more liquid, larger, more numerous, and often very foul.

One month before hospitalization the character of the stools changed so that thereafter they were usually large, somewhat foamy, grayish in appearance and exceedingly foul. The abdomen became more noticeably protuberant, the patient's disposition was noted to be constantly poor and his nutritional state was obviously failing.

Physical examination revealed a well developed but poorly nourished infant looking chronically ill. The muscles were moderately wasted, particularly in the buttocks and extremities. The abdomen was markedly protuberant, but no palpable masses were felt. The heart and lungs were normal. The throat showed enlarged tonsils with exudate in the crypts. There was a mucopurulent postnasal drip, as well as crusting in the nares. Stool examination showed a moderately watery, foul, grayish-colored movement, with no blood, pus or mucus visible. Cultures of the stools were negative. The urine was negative to ordinary examination. The leukocyte level was 14,000 per cubic millimeter with 85 per cent cells of the polymorphonuclear series, mostly of the band form. Cultures of the nose and throat showed many hemolytic *Staphylococcus aureus* in the tonsillar exudate, and a mixture of *Streptococcus hemolyticus*, *pneumococcus*, and *Staphylococcus aureus* in the cultures from the nasal swabs. Roentgenograms showed clouding of all the ethmoid and maxillary sinuses with thickened mucous membranes, but no retained secretions. The mastoid air cells also were somewhat clouded. In the lateral plate of the skull there was marked increase in the amount of adenoid tissue.

Because of the obvious foci of infection in the upper respiratory passages, including the tonsils and adenoid tissues, the patient was given saturating doses of sulfadiazine so that by the third day a level of 8 mg per 100 cc was present in the blood, and then careful removal of the large adenoids and tonsils was carried out. The sulfonamide therapy was continued after operation. Convalescence was entirely uneventful. The diarrhea subsided rapidly in the week after operation, and the patient was discharged at the end of this time on a free diet. In the following month there was rapid improvement in his physical condition and no return of the diarrhea even on a liberal diet, a few months after operation his weight was 25 pounds, and he appeared to be in excellent health.

*Comment*—This patient had suffered from chronic and recurrent nasopharyngitis, sinusitis and tonsillitis from the age of 12 to 20 months. Diarrhea had started at the time of the first acute infection and had persisted, off and on, for the following 8 months. There had been a loss of weight and other evidences of serious nutritional failure. Foci of infection were demonstrated in the tonsils and adenoids with probable persistent infection in the sinuses. A mixture of pathogenic organisms was cultured from these regions. Under chemotherapy the patient was subjected to operation for removal of the infected lymphoid tissue in the nose and throat. The patient made an uneventful recovery from this procedure, the diarrhea quickly improved and did not return, and within 2 months a gain of 7 pounds was recorded. The patient was able to take a normal diet in unlimited amounts. Here the picture of the celiac syndrome, as judged by wasting, abdominal distention and large foul stools, was the result of chronic and recurrent

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through some part of the small intestine. Palpation of a large, thickened colon may suggest the true megacolon. Changes in the size, rate and rhythm of the heart and the presence of characteristic murmurs may help establish the diagnosis of congenital heart disease. Enlargement of the kidneys as palpated through the abdominal wall or in the flanks may indicate anomalies and secondary infection in this system.

The presence of congenital abnormalities of the eyes, the nose and the mouth, the hands or the feet is so often associated with congenital anomalies of the internal organs that these should be thoroughly investigated when external malformations are noted.

*Roentgenographic examination* is an important adjunct to the establishment of the diagnosis of congenital anomaly as a cause for chronic diarrhea. Gastro-intestinal series and studies following the ingestion of barium by mouth, as well as the injection of barium by enema, may quickly serve to localize an area of obstruction in the intestinal tract or malposition of the cecum with the suggestion of malrotation and abnormality of the mesenteric attachment of the small intestine. Should this be found, further investigation may be spared the patient. If the gastro-intestinal tract appears normal and there is any suggestion of abnormal elements in the urine, intravenous pyelograms with diodrast or a similar opaque material should be performed. Should the results not be satisfactorily reassuring, even retrograde pyelography should be considered in an effort to rule out the genito-urinary system as the site of an anomaly. Roentgenograms of the heart, the lungs and the long bones likewise may serve as important evidence of the normal state of these organs, and are important steps in the exclusion of congenital anomalies as a cause for chronic diarrhea.

**Treatment**—In malrotations of the intestinal tract, whether they be incomplete rotation of the cecum or lack of attachment of the mesentery along the posterior abdominal wall or a completely rotated cecum which is mobile and unattached, treatment consists of operative interference as soon as the diagnosis is established. Failure to correct this anomaly commonly leads to midgut volvulus with symptoms of acute obstruction which if not corrected may produce death of the patient.

In the treatment of Hirschsprung's disease, or congenital megacolon, conservative measures such as the use of mineral oil and colonic lavages may often produce improvement in the chronic constipation which alternates with periods of diarrhea. Also, dilatation of the anal ring may offer relief to some children. Parasympathetic nerve stimulants have been tried to augment the activity of the colon, with only fair and variable success. Surgical procedures are therefore frequently necessary. The type and extent of operation is dependent upon the judgment of the surgeon. Cecostomy, resection and sympathectomy have all been advised in various cases.

In the treatment of anomalies of the genito-urinary tract, measures

the cases of schizophrenia in its early period. The best figures available at the present time are a result of a careful survey made by a special commission appointed by the Governor of the State of New York. The results of this survey, which compared the outcome of treated cases with a control group as similar as possible but which did not receive insulin shock therapy, indicated that the patients treated had about one and one-half times a greater probability of leaving the hospital greatly improved, if not recovered, that they had a greater chance of remaining well than had the control group, and if they did relapse improvement again was more likely to occur in those originally treated. It may, therefore, be given as a working hypothesis that patients with schizophrenic disorder have a certain recoverable tendency which may be materially increased by this type of treatment.

*Convulsive shock therapy* was originally introduced by von Meduna. Convulsions were produced by the intravenous injection of metrazol. Later a modification of the method of producing the convulsions by passing an electric current through the brain was perfected by Bini and Celletti. Convulsive shock therapy has proved to be of great value in terminating depressive and agitated states. In typical instances of the depressive phase of the manic-depressive psychosis four to twelve convulsive attacks will produce a complete cessation of the disorder in at least 80 per cent of the patients so treated. It also has a considerable value in terminating the disorder in patients in the manic phase. Its value is even more striking in the treatment of patients in the middle and older age groups suffering from agitations. In these patients the normal course of the psychosis is chronicity in almost 50 per cent and a long-continued psychosis of one to four or more years in the remainder, but with the convulsive shock treatment 60 to 70 per cent of these patients are quickly improved. In other words, many who would otherwise be incurable are made well, and many who would have a very long period of mental disorder are returned to good functioning capacity and happy contentment in the course of a few weeks at most.

The *prefrontal lobotomy* operation has not been used long enough nor has it been done in sufficient numbers to indicate with certainty the cases in which it offers the most benefit. Nevertheless, one can state that it offers a high probability of affording relief and returning to a much better status of efficiency and joy of living many of the chronic agitated patients who respond to no other form of treatment. Further, one finds that not a few chronic schizophrenic patients are greatly improved. It also has a distinct value in certain severely disturbed obsessive-compulsive neurotics. Many patients of this latter group in which all other forms of treatment, including long periods of psychotherapy, insulin and convulsive shock therapy had failed, have been greatly improved by the lobotomy operation. This operation, of course, is a very mutilating one which destroys to a considerable extent the integrity of the brain and does some damage to the



rotation of the cecum with partial obstruction to the passage of barium from the distal ileum into the colon

Eight days after entry, abdominal exploration was performed. The malrotation of the cecum was corrected by Ladd's operation, the partial obstruction of the ileum relieved, and the appendix removed.

Following operation, the patient had an uneventful convalescence. Within seven days he was exhibiting a voracious appetite, there was no apparent abdominal discomfort and the stools were normal. At no time thereafter were his bowel movements numerous or foul, and no limitation in diet was necessary.

*Comment*—This patient's diarrhea had persisted for 8 months and had shown little improvement on medication or after dietary changes. In the past history, the frequent vomiting during the first year of life was a significant finding. This in addition to abdominal pain and prominent intestinal patterning were somewhat suggestive of partial obstruction in the gastro-intestinal tract. Careful physical and laboratory examination excluded chronic infection as a basis for diarrhea. The flat glucose tolerance test suggested delay in emptying of the stomach. Roentgenograms revealed the nature of the difficulty and the underlying cause for his earlier vomiting and later diarrhea.

Malrotations of the intestinal tract often produce vomiting and diarrhea though one or the other may be more severe. Correction by surgery is necessary. Thereafter, complete relief may be expected. Within a short time, the patient is able to take a free diet and no further diarrhea is noted.

#### PANCREATIC FIBROSIS

Since 1938, there has been recognized and isolated from the cases ordinarily called celiac diseases a group of cases with absence or gross deficiency of pancreatic secretion, resulting in the early onset of diarrhea of the fatty type, failure to gain and often wasting, and the development of chronic respiratory infection, particularly recurrent bronchopneumonia, leading to the death of the patient. This condition has been named pancreatic fibrosis or cystic fibrosis of the pancreas. It is a congenital and often familial disturbance, and tends to manifest symptoms in the patient at an earlier age than the ordinary celiac disease of the type first described by Gee.

The *symptoms* of this condition may be failure to gain, even with an adequate dietary intake, abnormal stools, these being fatty, foul, and frequent, and chronic respiratory infections. As has been pointed out by Farber, the earliest evidence of this congenital deficiency in the pancreatic enzymes may be meconium ileus. However, usually the patient may do well for several months and then begin exhibiting diarrhea followed by failure to gain in weight or actual loss in weight. It is then noted that frequent respiratory infections with persistent cough and periods of feverishness are prone to occur. Sometimes the cough becomes so severe and paroxysmal that pertussis is suggested. Gradually more noticeable wasting then occurs. The large, bulky,

first symptom in her mother's case. Upon our patient developed the responsibility of insisting that her aunt be operated upon. The pathological examination indicated that the growth was benign.

Following this experience our patient began to complain of great fatigue, had disturbed sleep and began to worry about her somatic state. She complained of pains in various parts of her torso, began to fear that she herself had a malignant disease. She was hospitalized for two and one-half weeks in one of our best general hospitals. A painstaking inventory of her anatomy and physiology was made. X-rays, blood tests and almost every known laboratory procedure were given her. At the end of the two and one-half weeks of observation and examinations the diagnosis of psychoneurosis was offered and was confirmed by the psychiatrist.

Rather intensive psychotherapy was carried out by an able psychiatrist for two and one-half months without improvement. It was then considered advisable to transfer her to another psychiatrist who worked with her for several weeks more, when her symptoms became more marked. Agitation became so evident that she was admitted to the Boston Psychopathic Hospital. At the hospital a diagnosis of an agitated depression was made. Consequent upon this diagnosis, convulsive shock therapy was given. At the end of one week, after three convulsive treatments, the patient was greatly relieved, and after nine such treatments the patient was a gay, happy, unconcerned woman, able to take her place at home, with practical freedom from symptoms, and once more enjoying life to the fullest.

It seems indeed probable that had the correct diagnosis been made early, convulsive shock treatment applied at once would have resulted in the prompt alleviation of all symptoms and thereby saved the patient much suffering and disability. It would also have saved many hours of physicians' time. On the other hand, had the diagnosis of psychoneurosis been the correct one it would have been inexcusable to have given convulsive shock therapy.

Perhaps an even more striking case is that of a 53 year old, unmarried woman who came to the Boston Psychopathic Hospital after several months of increasing disability and discomfort. On entrance to the hospital the patient was complaining bitterly of gastric distress, nausea, vomiting and distaste for food. She likewise complained of headache, mild dizziness and generalized aches and pains. She slept very poorly, was constantly requesting sleeping drugs, and even with fair amounts of these slept but little each night. She presented a syndrome with which we are all so familiar, namely that of the complaining, whining, distressed neurotic.

However, we had known this patient at the hospital previously. Twenty years ago she had been a patient here for fourteen months, with rather similar symptomatology. Prolonged and intensive psychotherapy of fourteen months' duration accomplished little or nothing and she left the hospital to remain at home an invalid for another two years, so that her total illness on that occasion lasted more than three years, during which time she was incapable of looking after herself adequately, certainly incapable of work, and suffering much torture.

Nor was this her first disability—in fact, at the age of 16 she had had a long illness diagnosed as a psychoneurosis.

Her history indicated, however, that these disorders, in contrast to the usual story of the typical psychoneurotic, were distinctly delimited, and in the long intervals between these attacks she was a very able, hard-working, energetic person.

and stringy and quite cloudy. Actual analysis shows a diminution to a very low level, if not complete absence, of lipase as well as of amylase. But, most characteristically, trypsin is absent, in fact, test for this enzyme alone is sufficient to establish the diagnosis, since it is always absent in cases of pancreatic fibrosis and present in other cases. A simple test for tryptic activity may be carried out with a fresh unexposed x-ray film. The gelatin emulsion on this will be digested in half an hour by the trypsin present in normal pancreatic juice. This is tested for by placing two drops of the unknown juice on the film and observing in serial dilutions at the end of an hour.

**Treatment**—Treatment in its present experimental state is directed toward supplying food substance which can be absorbed and utilized without the need of pancreatic activity to any great extent. For this purpose the recently produced casein hydrolysates can replace milk as the basic food for such children. Nutramigen\* which contains casein hydrolysate in amino acid form, with the addition of dextrin, maltose and olive oil, should theoretically be an ideal food. In addition, it is desirable to supply a high intake of the various vitamin A and D concentrates in sufficient amounts to allow freedom from deficiencies even if only a small fraction of the material is absorbed, large doses of vitamin C in the form of ascorbic acid and vitamin B complex concentrates. It has seemed logical to offer a substitute for the absent pancreatic enzyme in the form of pancreatin, the dry extract of the normal pancreatic substance of the pig. However, destruction of this enzyme in the stomach has necessitated giving this material in enteric-coated form which may be difficult for the infant and the small child to swallow. In addition, tremendous amounts are necessary to replace, even to a small degree, the normal amount of pancreatic juice secreted by the healthy individual.

In the experimental treatment of this condition it has been suggested that increasing the tone and motility of the small intestine may improve absorption of vitamin A as well as food elements from the diet. With this in mind, prostigmine has been advised and tried both parenterally and orally in addition to the other measures detailed above. Finally, in the treatment of the secondary infections, particularly *Staphylococcus aureus* infections, bronchopneumonia and bronchiectases, the use of penicillin may offer greater hope for the improvement if not for the eventual recovery of such patients who regularly have succumbed to pulmonary infection in the past.

**CASE III**—A 25-month-old girl was brought in because of constant diarrhea since early infancy.

The family history was significant. There had been five pregnancies resulting in normal full-term infants. The first two children were well and symptom-free. The third child had died when four days old with evidences of intestinal obstruction. Postmortem examination was not performed. The fourth child suc-

\* Mead, Johnson & Company

are frequent disorders. While such assumptions would be unjustified on the basis of this small amount of selected material, yet such are the facts. Mild depressions are more common than most people realize; in fact, they are one of the most common disorders to be met in any clinic due to the fact that the early presenting symptoms are so often related to somatic complaints. The disorder frequently begins with the patient complaining of fatigue, headache, dizziness, visual difficulties, loss of appetite, various gastro-intestinal symptoms, shortness of breath and fear of various diseases. It is unquestionably a fact that many therapeutic successes are more the result of the spontaneous recovery of the depression which has been erroneously diagnosed than of the success of treatment, whether medicinal or psychotherapeutic in kind.

As the last case suggests, the diagnosis of schizophrenia is also often incorrectly made both positively and negatively. Schizophrenia often starts with symptoms that closely resemble the psychoneurosis. It is very common to find a psychoneurotic-like syndrome as the premonitory symptoms of the schizophrenic disorder continuing for many months before the more sinister symptoms are readily evidenced.

M. S. at the age of 17 began to be disturbed about sensations around his heart. In the course of a year he saw several internists who, after careful examination of the cardiac organ, assured him that there was no organic disease. This assurance had no effect upon the patient. He continued to worry and fret about his heart, became more and more concerned therewith, quit work and became increasingly irritable. It finally became evident that he was suffering from schizophrenia. After six years in a state hospital for mental disease, during the latter two of which he was completely mute, a bilateral lobotomy operation was performed, with a moderate degree of improvement. He then told the story that his original concern about his heart was instigated because he believed that he had been damaged through the means of an evil eye.

Although the value of bilateral lobotomy in the treatment of schizophrenia has not as yet been well established, it seems not unlikely that in many instances it is the treatment of choice. An early diagnosis for the proper evaluation of treatment, whether convulsive shock, insulin shock or lobotomy, is as important in this disorder as in any other in the field of medicine.

Diagnosis on which proper selection of therapy depends is important in psychiatry as in other fields of medicine. However, as the delay of a few weeks in the institution of therapy is not of critical importance, one is able to have a considerable period of observation and study of patients before coming to a final decision. During such a period of study one is actually beginning psychotherapy. The relationship of physician and patient is a most important portion of the therapy. Likewise, the interviews which represent an essential and basic part of the examination method are in themselves therapeutic. In the process of the examination the patient has the opportunity to

common in this and unusual in other types of chronic diarrhea. Next, cough, rapid respirations and occasional cyanosis were noted. Often the parents state that the patient is subject to frequent "colds" which fail to clear up completely. Sometimes, the cough is paroxysmal and ends in a "whoop" suggesting pertussis. Periods of acute exacerbation with high fever and signs of extending pneumonia are typical. In the unrecognized case of pancreatic fibrosis, these may be considered unrelated and accidental pneumonic infections.

In the advanced case, here illustrated, the constant cough, dyspnea and cyanosis, together with the persistent diarrhea, suggest the diagnosis of pancreatic fibrosis. The roentgenograms of the chest are quite typical. The finding of scant duodenal juice, thick and stringy in appearance, acid in reaction and lacking in the pancreatic enzymes, particularly trypsin, finally establishes the diagnosis.

### ALLERGY

In the consideration of allergy as a possible cause for chronic diarrhea in infancy and childhood it must be pointed out again that the routine steps necessary to eliminate the causes mentioned previously, namely, infection, congenital malformation, and cystic disease of the pancreas, should be followed in most instances. The high incidence of allergic manifestations of one sort or another, the commonly obtained history of allergy in other members of the patient's family and the frequent association in the minds of the parents of the onset of diarrhea with some particular food make it tempting to consider allergy as a first rather than fourth cause for diarrhea and to carry out tests for sensitivity or even immediately to start an elimination diet in an effort to improve the patient's bowel difficulties. Such short cuts may lead to prolongation of the complaint and loss of time in establishing the correct diagnosis. However, having obtained satisfactory evidence that the patient does not suffer from chronic infection, has no congenital malformation discernible by physical examination or roentgenographic studies, and has a normal vitamin A or, more important, pancreatic enzyme test, an allergic basis for chronic or recurrent diarrhea may be entertained.

**Diagnosis**—A striking familial history of allergy may be obtained in a high percentage of cases of chronic or recurrent diarrhea. It is more important to note such positive family history in the immediate relatives, that is, father, mother, and siblings, rather than in grandparents or aunts or uncles who may suffer from asthma or other allergic manifestations in adult life. The presence of typical skin rashes, such as eczema and urticaria, is also suggestive evidence of an allergic background in the patient. In the history, observation by the mother of swelling and edema about the lips and mouth shortly after the ingestion of one or another food is important. The complaint of abdominal pain and then

## ACTIVE IMMUNIZATION AGAINST SOME COMMON COMMUNICABLE DISEASES

MATTHEW A. DEROW, M.D.\* AND SANFORD B. HOOKER, M.D.†

THE number of infectious diseases against which specific protective measures are available is increasing rapidly. In some the need for prophylactic immunization is limited to persons of special occupational or geographical groups. Thus, inoculation against yellow fever is hardly of interest to residents of regions where the specific mosquito vector is absent. Similarly, Rocky Mountain spotted fever is a risk only to those whose occupation or habitat exposes them to possible bites by infected ticks. In others of practically universal distribution eventual exposure to possible infection is likely for almost everyone. Many of these are the so-called "diseases of childhood," essentially because children form the largest group of nonimmunes. Adults are relatively free by virtue of immunity resulting from recovery from the clinical disease or from the stimulus of repeated subclinical infections. Prominent in this category are whooping cough, diphtheria, scarlet fever, measles, chickenpox, typhoid fever and smallpox. In some, particularly typhoid fever, smallpox and diphtheria, the decreased incidence of the disease as a result of improved sanitation and fairly widespread immunization lessens the chance of an adult's being naturally immune and makes imperative the acquisition of protection by artificial active immunization. In still others of comparatively low incidence the very high case-fatality rates make them serious problems in the event of possible infection. Tetanus and rabies are good examples of these.

Of the available procedures, therefore, certain ones stand out as highly desirable for routine application in the population at large. Those considered here are applicable in the prevention of smallpox, diphtheria, whooping cough, scarlet fever, tetanus, the enteric fevers (typhoid and paratyphoid) and rabies. The first five of these diseases are of primary risk to children and protection should be established not later than the twelfth month of life. To delay immunization against these until the child's entry into school is to deny protection when it is most needed, as by far the majority of deaths occur in the pre-school ages. With the present large shifts of population and the habit of vacationing in localities whose state of sanitation may be at best doubtful, more widespread immunization against typhoid and paratyphoid fevers is advisable. Antirabic vaccination is a special prob-

\* Instructor in Bacteriology and Immunology, Boston University School of Medicine; Consultant in Pathology, Norfolk County Hospital, South Braintree.  
† Professor of Immunology, Boston University School of Medicine; Immunologist, Massachusetts Memorial Hospitals; Member, Evans Memorial, Boston.

The bowel movements then became somewhat pasty, foul and large in size. Irritability was a marked symptom and abdominal pain was apparent once or twice daily. Limitation of and changes in diet produced very little improvement in these symptoms. The appetite continued fair and the weight gain was slow but regular.

Physical examination showed a fairly well developed and nourished girl with no evident loss of subcutaneous tissue nor wasting of musculature. There was no evidence of acute or chronic infection, the abdomen was somewhat protuberant. There were no palpable viscera nor masses.

While under observation the patient was afebrile. The outstanding finding was the presence of mucus in the stools, which were only semi-formed. Cultures revealed no pathogenic organisms in the feces. Blood agglutination tests against the ordinary intestinal pathogens were negative. The blood and urine examinations showed normal findings. The glucose tolerance test was essentially normal. Studies of the vitamin A absorption and of the pancreatic enzymes both yielded normal results. Roentgenograms showed no abnormality of the colon by barium enema, and gastro-intestinal series showed only slight clumping of the barium in the small intestines. On a free and liberal diet the child showed no evidence of fat intolerance, the stools being occasionally soft and full of mucus, but more commonly normal in character. When given a diet of fat-free milk, curds, bananas, scraped beef and junket, the abdominal distention was less marked, and the patient did not complain as frequently of discomfort. She was therefore discharged for further care at home on this modified celiac-type diet.

During the following year, the patient had several attacks of abdominal pain followed by diarrhea containing much mucus. These could not be related to acute infection or dietary indiscretion. When re-examined at the age of  $3\frac{1}{2}$  years, the nutritional state was good, but the abdomen was still protuberant. At this time a leukocyte level of 20,000 per cubic millimeter was found, of which 15 per cent were eosinophilic polymorphonuclear cells. This, in association with the recurrent mild eczema of long standing, suggested an allergic disturbance. Scratch tests with the common food and inhalant antigens showed no significant reactions.

Three months later when the child was 3 years and 9 months of age, re-examination disclosed no new findings. There had been intermittent diarrhea and the stools continued semi-formed, somewhat foul and occasionally full of mucus. The eosinophilia persisted. Another fluoroscopic examination of the gastro-intestinal tract following barium ingestion showed increased peristalsis of the stomach and small intestines. The colon appeared normal. At this time the patient related that she experienced severe intestinal cramps after taking certain foods, especially those containing egg. Intradermal tests with numerous antigens revealed marked reactions to wheat, egg, orange, tomato and peas. A diet was prescribed substituting oats and rye for the wheat, ascorbic acid for the orange juice, and other vegetables in place of the known offenders. Within a month of this change, the mother reported marked improvement in the child's disposition and bowel movements, and freedom from abdominal discomfort.

In the ensuing year, the patient had occasional bowel movements which were soft and contained mucus, but on the whole she seemed greatly improved.

*Comment*—This child suffered from a recurrent diarrhea, the chief feature of which was the large amount of mucus in the bowel movement. There was no wasting nor diminution in growth and development. The strong family history of allergy and the mild eczema from which the patient suffered in early infancy suggested an allergic state. Physical examination showed relatively little alteration from normal excepting for abdominal prominence. All the laboratory evidences helped to rule out infection, congenital malformation or pancreatic

of material introduced, or subsequent slight edema or induration is kept to a minimum. Injections in a series should be alternated from arm to arm so as not to cause irritation by repeated inoculation into the same site. Inadvertent intravascular injection of some materials may give rise to disagreeable (occasionally serious) reactions. To prevent this, tension should be exerted on the plunger of the syringe after insertion of the needle beneath the skin. If blood appears in the hub of the syringe the needle is withdrawn and injection is made at another site.

Preparation of the site of injection requires surgical sterility. Diluted tincture of iodine (wiped off with alcohol to prevent possible burns) or the organomercurial tinctures are satisfactory for this purpose.

5. Individualization of treatment is a *sine qua non* in producing immunity with minimal discomfort to the subject. Printed directions must be considered as general guides to effective dosage, not as rigid, inviolable dicta. Where possible, precautionary tests should be done and as in all medication dosage should be modified in accordance with the age and weight of the patient. Above all, after one dose subsequent doses must be guided more by the previous reactions than by the printed label.

In order intelligently to individualize treatment one must have knowledge not only of technic but also of the nature and mode of action of the materials used. It is from this point of view that the following summaries have been prepared.

#### DIPHTHERIA

**Principle.**—Active immunity against diphtheric toxin is produced by the injection of toxoid or toxin-antitoxin.

**Material.**—1. *Toxoid* is toxin that has been modified so as to destroy its poisonous properties while retaining its ability to evoke antibody formation. In practice this is usually accomplished by prolonged incubation with dilute formaldehyde. For use in immunization against diphtheria, toxoid is usually standardized to contain 15  $L_t$  doses per cc., although concentrations as high as 45  $L_t$  doses per cc. have been used. Diphtheric toxoid may be used unaltered as *fluid toxoid* or as *alum-precipitated toxoid*. The latter is toxoid that has been precipitated with sterile alum to yield a suspension of insoluble alum-toxoid flocules. Toxoid is best kept at 5° C. (40° F.) but is not rendered dangerous for use by inadvertent freezing.

2. *Toxin-antitoxin* consists of a slightly underneutralized mixture of diphtheric toxin and antitoxin. Most preparations are made with equine antitoxin, but both ovine and caprine sera are in use. Experimental mixtures using human antitoxin have been prepared but have not received widespread trial. The mixture contains 0.1  $L+$  dose of



The vitamin A tolerance test usually discloses a poor absorption of fat, but again this is not absolutely diagnostic of celiac disease. Pancreatic fibrosis must be excluded by examination of the duodenal juice for the pancreatic enzymes, particularly trypsin. At present, only by this method of elimination of all the previously mentioned conditions, is the diagnosis of celiac disease established.

**Treatment**—The old and well established method of dietary treatment of patients with celiac disease still remains the basis for successful handling of such patients. This consists of limitation of the patient's food intake to a simple basic diet low in fat and high in protein. Such a diet is continued until the patient develops constipation, shows improvement in appetite, in disposition and in abdominal distention, and begins to gain weight. When all of these changes have been established, the diet is gradually increased by the addition of foods, low in fat, in order to satisfy the patient's increased appetite and improve the tolerance to new foods. Each food must be added cautiously, in small amount, one new item at a time, and continued only if the patient seems to tolerate it well, that is, if there is not recurrence of diarrhea, of abdominal discomfort or distention or of irritability. Attention must be paid to the need for adequate vitamin supplements, as well as iron to offset the deficiency of this mineral in the restricted diet. The patient often gains rapidly on these simple but well-tolerated foods, and seems to accept and enjoy the rigid monotony of the diet for long periods of time, much to the parents' amazement.

The diets for patients with celiac disease have been divided arbitrarily into three states. The basic regimen consists of

- 1 Thirty-two to 40 ounces of skimmed or fat-free milk, or skimmed lactic acid milk, or protein milk, usually prepared from protein milk powder. Dextrose or saccharine may be added to the sour milks to improve the taste. The former has the advantage of adding calories to the diet, often a necessary step.

- 2 Dry skimmed milk curds,  $\frac{1}{4}$  to  $\frac{1}{2}$  pound a day, puréed through a coarse strainer and divided into three meals. These can be obtained from the larger dairy companies. They can also be prepared in the home by coagulation of skimmed milk with rennet tablets and then draining the coagulant for several hours in the refrigerator, until the curd is thoroughly dried.

- 3 Ripe bananas, three or more per day, as required to satisfy the child's appetite. These are usually well tolerated by patients with celiac disease.

- 4 Vitamin supplements including, daily, at least 20 or 30 drops of cod liver oil concentrate, 50 to 100 mg. of ascorbic acid, and at least 3 teaspoonfuls of vitamin B complex (Lederle) or some equally potent liver extract vitamin B preparation.

As May and others pointed out, the injection of parenteral vitamin complex and crude liver extract often accelerates the patient's im-

## PERTUSSIS

**Principle.**—Active immunity is produced by the injection of a suspension of dead bacteria.

**Material.**—Vaccines are prepared from smooth (Phase I) recently isolated cultures of *Haemophilus pertussis*. The cultures are grown on agar plates or slants enriched with human blood, harvested, and suspended in saline solution containing phenol as a preservative. The concentration of the suspension varies with different laboratories. The vaccines usually available contain:

10,000	million organisms per cc.	—“single strength”
15,000	“ “ “ “	—“medium strength”
20,000	“ “ “ “	—“double strength”
40,000	“ “ “ “	—“superconcentrate”

Alum-precipitated vaccines are prepared according to the same basic method and then treated with alum to decrease the rate of absorption after injection. These are usually standardized to contain 15,000 million organisms per cc.

In addition to the vaccines described, which have been most widely used, two other preparations are in use. One consists of a suspension of killed *H. pertussis* combined with an “endotoxoid” prepared by treatment of an extract of the organisms. The other is prepared from the soluble toxin of the organism by treatment with formaldehyde to yield a detoxified antigen or toxoid. Both have been reported as satisfactory immunizing agents.

**Method.**—A total of 80 to 100,000 million organisms administered in three or four injections over a period of six to eight weeks is required for effective prophylaxis. The actual volume of vaccine varies with the concentration of the preparation used.

1. *Plain Vaccine.*—The schedule which follows is for a suspension of 20,000 million organisms per cc. One, 2 and 2 cc. injected subcutaneously at intervals of three to four weeks constitute a course. In older children the last dose may be increased to 3 cc. (usually divided into two injections of 1.5 cc. in each arm). With a more concentrated suspension the volume should be decreased in proportion. More dilute suspensions require an additional dose or two to avoid injections of unduly large volume.

2. *Alum-precipitated Vaccine.*—Three doses of 0.5 cc. are administered subcutaneously at three- to four-week intervals. Although the total dosage is only 45,000 million organisms the enhanced action of the precipitated vaccine gives rise to a satisfactory immune response.

**Comment.**—There is no apparent benefit to be gained by the use of vaccines of low concentration that might outweigh the unavoidable increase in number or size of injections. Reactions following the use of the more concentrated vaccines are neither more frequent nor more severe than those associated with the dilute preparations, whereas the

Roentgenograms revealed poor bone growth and decalcification. Gastro-intestinal series showed clumping of the barium in the small intestines.

On a diet of protein milk, dry curds and accessory vitamins, the patient's stools diminished in number and lost their foul and foamy appearance. At first, there was a reduction in weight to 15 pounds, but after a 3-week period of adjustment there was a slow but steady weight gain. Vitamin B complex (Lederle) was given intramuscularly, 2 cc per day for 10 days, and then orally, 1 teaspoonful three times daily. The patient's disposition and appetite improved. The abdominal distention diminished. He was then sent home, with the addition to this basic diet of banana, scraped beef and egg yolk. In the following 6 months there was steady increase in weight so that at 3 years he was up to 28 pounds. Rice, green vegetables and other desserts were gradually introduced into the diet and taken well. There was only one re-exacerbation of the diarrhea, in association with an acute respiratory infection. Temporary restriction in food intake produced prompt improvement following this disturbance. Up to the fourth year the patient continued on a diet limited only as to fats and coarse vegetables, he was gaining and was symptom-free.

*Comment*—In this case the chronic diarrhea was associated with typical foamy, fetid, light-colored stools, wasting of the muscles, poor disposition, anorexia and the other symptoms first described by Gee. It is of interest here and of possible relationship to the onset of the diarrhea in this susceptible infant that soft solid foods were started very early in life, as seems to be the custom in some pediatric practices at present. It has been shown that amylase, particularly, is deficient in the pancreatic juice of even normal infants under 3 to 5 months. It may be unwise therefore to burden the intestinal tract with excessive amounts of soft-solid foods before this time, especially if the infant shows a tendency to loose or numerous bowel movements. In the case here quoted, acute and chronic infection, congenital malformation of the gastro-intestinal tract, pancreatic fibrosis and other basic conditions were excluded as the cause for the chronic diarrhea. Treatment with a strict celiac diet, with the addition of vitamin B complex intramuscularly, and then orally, as suggested by May, produced slow but satisfactory response. The infant continued to improve and do well, even as additional foods were introduced. During an intercurrent acute infection, the diarrhea returned. This is commonly seen in patients with celiac disease and necessitates a return to a limited basic celiac diet, even after the infection subsides, until the bowel movements become normal again. Thereafter foods can be re-introduced cautiously, as in this case.

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tions of 2 cc. usually constitute a course of treatment. In cases with severe bite wounds, especially about the head, seven additional injections are advisable.

Treatment with the Pasteur vaccine consists of sixteen to twenty-five daily injections of vaccine of increasing virulence. The first eight injections use preparations of cord dried four days; the next eight utilize two-day cord; the last nine are usually two- or three-day cord suspensions.

With either preparation the vaccine is administered subcutaneously, usually over the abdomen, the site for each dose being separated as far as possible from that of the previous. A convenient method is to mark off the abdomen into quadrants through the umbilicus, the daily sites being chosen by a clockwise rotation through the quadrants.

**Comment.**—Local treatment of the wound is an essential part of prophylaxis against rabies. Cauterization with nitric acid is an effective and time-honoured procedure. However, recent comparative studies\* would indicate that less drastic measures such as thorough cleansing with 20 per cent green soap solution followed by the application of tincture of iodine are probably just as effective. The latter method may well be seriously considered in more superficial bite-wounds especially about the face where the traditional treatment may leave disfiguring scars.

The risk of contracting rabies following the bite of a rabid animal, despite prophylactic immunization, varies from approximately 1 chance in 75 to 1 in 4500 depending on the depth and location of the bite. Wounds on the head are the most dangerous, those on the trunk and legs least so.

The administration of the vaccine (especially attenuated virulent vaccine) is not without a certain risk of its own. The most serious complication of treatment is postvaccinal paralysis, which may be of prolonged duration or even fatal. The incidence of such accidents of treatment is 1 in 3400 with attenuated cord virus and 1 in 8900 to 17,000 with killed vaccines. Paralytic complications seem to be associated with strenuous physical exertion following antirabic prophylaxis, and such patients should be cautioned against undue physical activity. However the treatment should not interfere with the normal daily activities of most people.

(For a comprehensive discussion of the problems of the control of rabies the reader is referred to L. T. Webster's "Rabies," The Macmillan Company, New York, 1942.)

#### TETANUS

**Principle.**—Active immunity against tetanal toxin is established by the injection of tetanal toxoid.

**Material.**—Toxic filtrates of cultures of *Clostridium tetani* are treated with formaldehyde, yielding tetanal toxoid which lacks the poisonous

\* Shaughnessy, H. J. and Zichis, J.: J.A.M.A., 123:528, 1943.

# TECHNIC OF INTERVIEWING A PATIENT WITH PSYCHOSOMATIC DISORDER

STANLEY COBB, M D \*

## DEFINITIONS

BEFORE beginning this clinic it is important to agree on certain definitions, because many of our medical disagreements are due to lack of care in the use of terms To begin with, broadly speaking, *all* disorders of the human organism may be psychosomatic to some degree, because all organs are reached by nerves and to some extent affected by nerve impulses Thus the more complex levels of the central nervous system (the "psyche" or psychological levels) can cause physicochemical effects upon tissue by way of the chains of neurons connecting cerebral cortex with, for example, synovial membrane, bladder, gut, adrenal, heart or skin There is a mechanism that can conduct nerve impulses to any disordered organ for good or ill Whether or not such phenomena occur clinically to any significant degree and with any regularity is the important point To a large extent the problems of psychosomatic medicine involve the relationship of the highest levels of cerebral integration, through the autonomic and endocrine systems, to the organs affected Of the organs affected by the higher nervous center, we must omit the nervous system because a study of the relationship of higher nervous levels to lower, all within the nervous system, would simply be neurology, and psychosomatic medicine obviously cannot take in the whole of neurology Nor can the effect of memory, learning, emotions, etc., upon motor behavior be called "psychosomatics", that is psychiatry As I have said elsewhere "Psychosomatics is by its etymology a liaison field between neurology, psychiatry, and medicine Its data consist largely of what is known concerning emotions, feelings, autonomic neurology, and related medical symptoms [The pseudoneurological phenomena of hysteria are a disputed area which the present author would prefer to see left to psychiatry ] As well as I can define psychosomatic medicine now, it seems to be a clinical field that takes up the study of the abnormal functions set going by emotional stimulation in any system of the body (except the nervous system) and the study of the lesions caused by such abnormal functioning"<sup>1</sup>

## SCOPE OF PSYCHOSOMATIC MEDICINE

The diseases in which there is good evidence to indicate that emotions frequently disrupt normal physiological function to cause patho-

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From the Department of Psychiatry, Massachusetts General Hospital

\* Bullard Professor of Neuropathology, Harvard Medical School, Psychiatrist-in-Chief, Massachusetts General Hospital

Vaccines are also prepared containing larger numbers of the paratyphoid organisms.

**Method.**—The vaccine may be administered either subcutaneously or intracutaneously.

1. *Primary vaccination* by the standard *subcutaneous* method requires three injections of 0.5, 1 and 1 cc. at weekly intervals.

By the *intracutaneous* route primary vaccination requires three injections of 0.10, 0.15 and 0.20 cc. at weekly intervals.

Primary immunization by either method should be carried out two or three months prior to possible exposure to infection.

2. *Subsequent or stimulating ("booster") courses* of injections are required after two or three years to maintain immunity. (At least one repeat course is mandatory in the Army.)

*Subcutaneous method:* Repeat course as outlined above. If practicable one may administer a single dose of 0.5 cc. at yearly intervals.

*Intracutaneous route:* One intracutaneous injection of 0.10 cc. (This is accepted by the Army as a complete secondary or stimulating course.) It is preferable to repeat this dose every year if the risk of exposure is high.

**Comment.**—The success of the subcutaneous administration of typhoid vaccine is attested by its use in the armed forces in millions of individuals during the past thirty years. Since the institution of compulsory active immunization, typhoid fever has all but disappeared in the armed forces, whereas the incidence of dysentery which is spread in much the same manner has remained at a constant high level over the same period of time.

Severe reactions to the use of the vaccine in this manner are uncommon (under 1 per cent of cases) and usually consist of malaise, fever, anorexia, and rarely chills. Local reactions are more common and may give rise to considerable induration, edema and tenderness at the site of injection.

The intracutaneous method of administration has not been used in as many cases or over so long a period of time. Recent well-controlled studies indicate that following primary immunization by this method the absolute height of antibody production is not quite as great as with the older method. However, the immunity induced is probably adequate for protection against all but unusually massive infections. This disadvantage as compared to the subcutaneous route may be overcome by increasing the number of injections or lengthening the interval between injections. Reactions of a systemic nature are extremely rare, and local reactions usually consist of a transient induration, erythema, and slight tenderness at the site of inoculation. The method lends itself well to individual as opposed to mass immunization.

logical function and sometimes lesions, can be catalogued in a brief space. Halliday has made a good list in his excellent paper<sup>2</sup> and I combine it with my own list<sup>1</sup> in the accompanying table

### TECHNIC

Faced, then, with a patient suffering from one of the above syndromes, what does the physician actually do?

He begins, as usual, with a bedside chat to make rapport with the patient, get an idea of the problem and an impression of the personality. This is done in an office or private room, not on the open ward. Talks between physician and patient in the hearing of other patients, nurses or others, give information of a certain kind, but the inhibition, embarrassment and sensitiveness of both the interviewer and patient distort the result and may lead to misinformation which starts the whole case off on the wrong track. Privacy is essential for any psychiatric interview. Quietly but firmly shutting the door is the best way of saying to the patient "This is between you and me." A properly introduced third person (a student, perhaps) may often sit in on an interview without doing much harm, but supernumeraries are to be avoided if possible.

To begin with, I usually say "Well, what brought you in to the hospital?" to start the patient off on his chief complaint. I may be met with the counter "The ambulance"—and have to take a new line, such as "I mean, what is your complaint?" perhaps to be countered again with "Oh, I have no complaint!" You may then ask "What is your trouble?" and the reply is "That's what I want to find out, doctor." So at last you have to ask "What is your chief symptom?" But even this preliminary sparring is important for diagnosis. The hysterical patient usually starts right off into the exposition you desire with a simple stimulus of one question. The patient who beats around the bush and bandies terms often turns out to be an obsessional neurotic.

Once the patient is started on his story let him lead, merely interjecting such words as, "Yes," "And then?" or "After that?" If the conversation gets into trivialities, it will have to be brought back to main themes. This is best done by picking out some important phrase the patient has spoken and repeating it back to him—for example "Vomited every morning?" or "Weak feelings all the time?"

The point is to get the story of the patient's present predicament as much in his own words and in his own order as possible. If this is done it is much more likely to be true than a story elicited by a set of stock questions. Many neurotic patients, when put through the mill of a regular routine "chief complaint, present illness, past history, occupational history, marital history, system review and habits" will react badly and say things that they do not mean, some of them actually untruthful and misleading. To get all this down in the record is

tentative and subject to modification, depending on the reactions of the individual being immunized. Slavish adherence to printed schedules negates the basic principle of individualization of treatment, and particularly in the case of scarlatinal prophylaxis has done much to discredit its use because of the uncomfortable and severe reactions that follow ill-advised dosage schedules.

The immunity produced by this procedure is *purely antitoxic* in nature and not directed against the streptococcus proper. Nevertheless, infections with scarlatinal streptococci in Dick-negative individuals rarely result in mastoiditis, suppurative lymph nodes, nephritism or cardiac involvement—complications that are so common in unmodified scarlet fever. One may say that in scarlet fever immunity to one aggressive weapon of the streptococcus is far better than no immunity at all. Sulfonamides have proved of tremendous value in the therapy of streptococcal infections, but one must not forget that they have no action against the toxic phase of the disease.

#### SMALLPOX

**Principle.**—Active immunity against variola is induced by inoculation with a live virus of a related disease (vaccinia).

**Material.**—Vaccine virus consists of a hemogenized glycerolated suspension of vesicular material from a calf that has been inoculated with vaccinia. After a "ripening" interval the vaccine is tested for potency and for the presence of anaerobic and virulent aerobic contaminants. Although absolute bacterial sterility is rarely achieved, the number of viable bacteria, chiefly nonvirulent staphylococci, is kept to a minimum by the addition of 0.5 per cent of phenol. The vaccine is packaged in sealed capillaries containing sufficient material for one immunization. The virus is very sensitive to heat and *must be kept continuously refrigerated, preferably below freezing*, until used. The freezing compartment of mechanical refrigerators is ideal for the storage of vaccinal virus.

Bacterially sterile virus can be produced by growth on chick embryos. However, such cultural methods result in the loss by the virus of some component essential for producing complete immunity in man and other mammals. Until this deficiency can be corrected by improved cultural methods, the traditional calf vaccine remains the agent of choice.

**Method.**—The site of vaccination is prepared by thorough cleansing with soap and water, followed by a volatile antiseptic such as ether, acetone or undenatured 95 per cent alcohol, which is allowed to dry. Under no circumstances should a nonvolatile disinfectant such as iodine, organic mercurials (mercurochrome, metaphen, merthiolate) or even denatured alcohol be used in the preparation of the site as the virus is readily inactivated by such reagents resulting in the failure of the vaccination to "take."



case with psychiatric factors, a note, I believe, comes nearer to the truth than the routine "Past histories, present illnesses, occupational histories," and so on, that fill most hospital record rooms. These long

CASE #16 ♀		Hospital # 319721		
		Date 1936		
YEAR	MEDICAL DATA	ARTHRITIS	SOCIAL DATA	AGE
			Born in New Brunswick	
1887			Fourth child	1
1900			Mother died Took care of children	14
1902			Began work outside of home	16
1906			Worked	20
1907			Married	21
1910			1st child born Worked intermittently	24
1913			2nd child born died	27
1914			3rd child born	28
1915			4th child born	29
1918			Feels bitter against husband 5th child born	32
1919	Mild arthritis in hip		Husband had appendicitis peritonitis	33
1920	Both hips affected		Housework and nursing for living	34
1921			Husband too lazy to support family Husband a devil	35
1922			Work	36
1923			Oldest child - T B	37
1924			Supporting sick child	38
1925				39
1926	Remission			40
1927			6th child born prematurely Daughter left school	41
1928	Arthritis in knees and wrists		Learned of husband's infidelity Stopped work	42
1929	Flexion deformity knees - wheel chair		Husband worked earned little	43
1930	Bed for a year		Child ill	44
1931	Worse		Very unhappy with husband	45
1932	Hospitalized Operation on knees			46
1933	Walking with braces Exacerbation			47
1934			Trip to Canada	48
1935	Exacerbation			49
1936	In bed		Feels has had an awful life	50

Fig 96—Life chart made as described in text

and meticulous accounts are often most laudable efforts, but one reads them through and misses the essential relationships. The forest is obscured by the trees.

For an example I give here a life chart (Fig 96) that gives an out-

It is seen, thus, that vaccination serves as a test of immunity to smallpox. As a test procedure it is unique in that in people who show no immunity it automatically remedies the defect. Primary vaccination should be performed in the first year of life, and the state of immunity tested by revaccination on entering primary school and high school and at intervals thereafter. Smallpox can be eradicated only by such a program of vaccination and revaccination of the entire population.

In persons with eczema or similar disseminated skin lesions vaccination is best postponed until the skin returns to normal, as generalized vaccinia may follow inoculation. However, *in the face of an epidemic or other likely exposure to smallpox there are no contraindications to vaccination.*

#### COMBINED IMMUNIZATION

Simultaneous immunization against more than one disease, using combined antigens, offers certain advantages. The saving in time and the smaller number of injections required are immediately apparent. Moreover there is considerable evidence that the immune response to such combined antigens is often greater against each than when separate inoculations are used. The reactions following administration of mixed preparations are not appreciably greater than those following the usual single antigens (especially in children) and they lend themselves particularly well to routine prophylaxis in pediatric practice. There are at present available a variety of mixtures for such combined immunization. The most widely used of these are:

Diphtheric and tetanal toxoids combined

Diphtheric toxoid and pertussis vaccine combined

Diphtheric and tetanal toxoids and pertussis vaccine combined

Tetanal toxoid and typhoid vaccine combined

As an exception, smallpox vaccination which involves the introduction into the body of a live dermatropic virus should preferably be performed alone. Any injury to the skin (even the insertion of a needle) may result in secondary vaccinia at the site of the injury. To guard against such complications, though the risk is perhaps small, other inoculations were best postponed until the height of the vaccinal reaction has passed.

case is fairly clear from the start, one has a much better chance of a good therapeutic result if one will have the courage to make a diagnosis forthwith and then proceed immediately to treatment

The treatment is best done in teamwork<sup>5</sup> with the medical man. He should know what is coming out in the interviews and what is being said by way of suggestion, and he should keep the psychiatrist in touch with the medical treatment. Close cooperation is often difficult, but necessary. Neurotic patients have an uncanny skill in playing one doctor off against another, unless the cooperation between the doctors is manifestly too much for him to assail.

#### SUMMARY

Psychosomatic medicine is defined and delimited in a practical way. A method of interviewing is described in which (1) privacy is essential, (2) the patient is made to lead the conversation, (3) direct questions are avoided, (4) note taking is limited and (5) social and medical facts are arranged on a life chart.

Therapy begins as soon as doctor and patient begin to talk together, so the physician must have in mind what he is doing in relation to "ventilation," "insight," "dependence" and suggestion.

The psychiatrist should work intimately and concurrently with the internist.

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Today this has been established as a well-known fact. In such cases the bone conduction may be reduced as well, even before there is much loss of low tones—a phenomenon also previously considered due to nerve deafness. The restoration of adequate ventilation of the middle ear by re-establishing patency of the eustachian tubes often results in a rapid return to normal hearing. This finding is easily demonstrated by the audiometer and tuning fork test. For this reason, many patients who previously had been classified as having a nerve deafness for which there was no satisfactory treatment, now fall into the category of treatable cases with good promise for restoration of normal hearing.

According to Crowe and Burnam,<sup>3</sup> 75 per cent of children who have had adenoidectomy performed before puberty have visible evidence of recurrence of such lymphoid tissue. The lymphoid nodules are an integral part of the mucosa of the pharynx and nasopharynx, and cannot be completely removed by surgery in any case. After the excision of the large mass of adenoid or tonsillar tissue, the small lymphoid follicles tend to hypertrophy, thereby producing the clinical appearance of "granular" pharyngitis or nasopharyngitis. Many of these nodules are in the region of the eustachian orifices or in the actual pharyngeal portion of the eustachian tubes—obviously inaccessible to surgical means. An increase of this tissue as a result either of infection, normal physiologic hypertrophy with growth, or as a response to surgical removal of masses of such tissue will produce partial occlusion of the tube with a resulting chronic tubotympanic catarrh. If left untreated, irreversible changes are produced in the middle ear which result in permanent catarrhal deafness for which there is no adequate treatment. After the age of fifteen years treatment is much less satisfactory because these secondary changes in the middle ear and tube may be so advanced. Therefore, treatment of the lymphoid tissue must be undertaken in childhood before these irreversible changes have occurred. This present discussion concerns the use of some form of radiation to destroy the lymphoid follicles and their lymphocytes.

It has long been known that lymphoid tissue is unusually sensitive to x-radiation and radium and for this reason can be inhibited by very small doses of these agents. The lymphocyte has a definite life cycle just as have cells of the skin, and the old lymphocytes progress outward into the crypts and are phagocytized, with new ones taking their places. Radiation prevents cell division and formation of new lymphocytes (Crowe and Baylor<sup>1</sup>). The germinal centers of the follicles are injured and obliterative changes of the endothelium of both blood vessels and lymphatics are produced (Schenck<sup>4</sup>). The amount of radiation is not sufficient to cause dryness or atrophy of the mucous membrane; it does not cause crusting in the mouth, pharynx or nasopharynx; it produces no skin changes, involvement of the pituitary or other untoward reactions. Repeated treatment, however, may be necessary to hold this tissue in check during the years of active pro-

**Functional Disorders of Menstruation**—From the end of adolescence to the beginning of the climacteric, the healthy mature ovary completes the cycle of follicular growth, ovulation and luteal activity in about 28 days, arbitrarily expressed as  $(28 \pm 2) \pm 2$  days, and the endometrium responds with flow on the 25th to the 33rd day.\* Within these limits, the normal individual usually, not always, completes the ovarian cycle in  $\pm 2$  days,  $\pm$  representing a single number within the range  $(28 \pm 2)$ . Often the sequence of maturation, ovulation and luteinization takes up more or less than  $\pm 2$  days in the normal woman. If so, it usually does this repeatedly, for many months or years at a time. For no woman, however, is  $\pm$  a constant. Many women have "short" cycles or "long" cycles. The resultant flow is in short or long cycles, but so long as ovulation occurs, bleeding is fairly cyclic. If this cyclic flow following ovulation takes place regularly within the limits  $(28 \pm 2) \pm 2$ , it is still to be considered typical and thus in order.

**TEMPORAL DEVIATIONS**—An habitual deviation from such limits of cycle length, provided ovulation occurs, is a functional disorder of menstruation, since it is caused by change in the length, and not the completeness, of the ovarian cycle. In other words, fairly regular post-ovulatory flow occurring habitually at intervals shorter than 24 days, or longer than 32 days, is occasioned by the breakdown of a predecidua built up by the normal sequence of ovarian hormones, estrogen and progesterone. The shorter type is called *polymenorrhea*, because there are more periods in the year than the usual thirteen, the longer type, *oligomenorrhea*, since there are fewer than thirteen of them.

**QUALITATIVE AND QUANTITATIVE DEVIATIONS AND THE FACTORS CONDITIONING THESE**—I shall discuss the nature of these temporal deviations and their treatment later. First we must consider differences in the *kind* of flow. The duration, amount and quality of all periods of functional flow are essentially similar in the individual female throughout many years. The over-all characteristics of flow may vary in one woman during different phases of her mature life, such as before or after marriage, or after parturition, or in succeeding decades, or when domiciled in different geographic areas, but from month to month they are closely alike. The determinants of these characteristics of flow—duration, amount and quality—are but ill-understood, indeed, many are doubtless unknown as such. They are, however, fairly constant for long periods of time.

The absolute amount of the estrogen which stimulates proliferation of the endometrium and establishes therein the bleeding potential is one of these factors, the amount of progesterone which conditions the metabolism of estrogen and its degradation, causes the proliferative endometrium to change into the predecidua, and enhances,

\* The cycle begins on the first day of menstruation and extends up to, but does not include, the first day of the succeeding flow.

sibly somewhat diminished, is more prolonged than the air conduction. It is best to use a tuning fork of 256 or 512 frequency, as lower pitched forks will produce too much vibratory sensation as well as sound. These tests should be supplemented by carefully performed audiometer tests. The curve of conductive deafness may be generally depressed throughout all tones, or it may be a low tone deafness with fairly good high tones. As mentioned above, many cases, however, show fairly normal low tones with fairly normal mid tones, but a marked falling off of the higher tones, even though there is no nerve involvement. An abrupt drop in any curve paralleled by a similar marked drop in bone conduction usually suggests a lesion of the cochlea or the nerve. In these cases, radiation is useless.

In the average child under four to five years of age, audiometric studies and tuning fork tests are quite unreliable, as considerable concentration and cooperation are necessary for proper evaluation of these tests. In such cases the word of the parent or kindergarten teacher is of great importance as far as the possibility of an existing deafness is concerned. Examination in a strange office may be rather frightening to the apprehensive patient, whereas the mother will know that at home the child cannot hear the radio unless it is very loud and cannot hear family discussions which undoubtedly would otherwise interest him. In such cases, investigation of the nasopharynx is just as important as if audiograms had shown typical conductive deafness curves.

#### TREATMENT

When the diagnosis of conductive deafness due to hyperplastic lymphoid tissue in the nasopharynx has been established, a decision as to the use of surgery or radiation must be made. If there is a sizable mass of adenoid tissue, it is usually best to remove it surgically. If this has already been done, it should be noted whether secondary hypertrophy of lymphoid follicles has occurred. If any of this tissue is present in or about the eustachian orifices where curettage would be impossible or dangerous because of the possibility of producing stenosis of the orifices, then radiation is advisable. Radon applied directly to the nasopharynx has been used in recent years with complete success (Crowe and Burnam,<sup>3</sup> Burnam<sup>5</sup>). Since 1939 we have been employing x-radiation with equal success, and the efficacy of this form of treatment has been confirmed by other clinics and investigators (Rentschler and Settle,<sup>6</sup> Caruthers<sup>7</sup>). X-ray therapy has several obvious advantages over the use of radium or radon. The necessary equipment is usually available in the smaller communities and hospitals as well as in the larger centers, and little skill or experience is required to obtain a completely satisfactory response, and sedation or anesthesia usually is not necessary.

Thirty-eight patients with conductive deafness have been treated

then functions for 14 days During the preovulatory phase, estrogen, which stimulates proliferation of the endometrium, is produced in increasing amounts From a short time preceding and during the 2 weeks after ovulation, the corpus luteum secretes estrogen and progesterone, the latter evoking in the endometrium those cytologic qualities denoting "secretion" or "function"

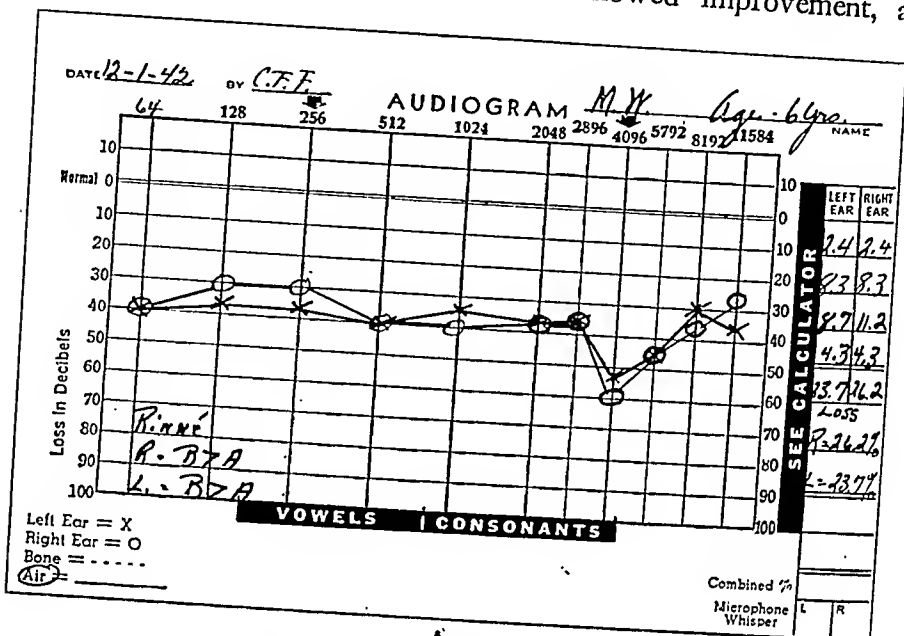
In *oligomenorrhea*, when periods of flow closely resembling each other in quality and duration occur at longer intervals than every 32 days, as for instance every six weeks or only every few months, the prolongation of the intermenstrual phase, as far as I have been able to discern, is invariably due to delay in the rupture of the follicle (ovulation)—never to protracted functioning of the corpus luteum For some unknown reason, either the pituitary hormones, which cause the follicles to grow, fail to appear, or, for equally obscure reasons, the ovaries remain insensitive to these hormones for variable periods My observations indicate, however, that once ovulation is accomplished, the corpus luteum goes into action and completes its function in 2 weeks Treatment of this delay in ovulation is discussed later

In *polymenorrhea*, postovulatory or functional catamenia habitually occurs in cycles of from 22 to 23 days, i e, menstruation starts on the 23rd or 24th day of the cycle\* As in *oligomenorrhea*, the flow is uniform in duration and quality The underlying disturbance is often to be found in a shortening of the time taken to achieve ovulation A sufficient number of carefully studied cases has not been analyzed to permit statement of what proportion of the instances of *polymenorrhea* are due to the speeding-up of follicle-maturation My guess is that this is so in not less than 50 per cent of the cases In these, it is important to note that ovulation occurs—as in typical menstruation and in *oligomenorrhea*—about 14 days before the first day of flow In these cases, however, it does not occur 2 weeks after menstruation begins, but in less time than this, i e, the follicular phase of the cycle is shortened, contrary to the situation in *oligomenorrhea* where, as mentioned above, this stage is lengthened The disturbance in this form of *polymenorrhea* is one of follicular activation to which curative treatment, if any, should be directed

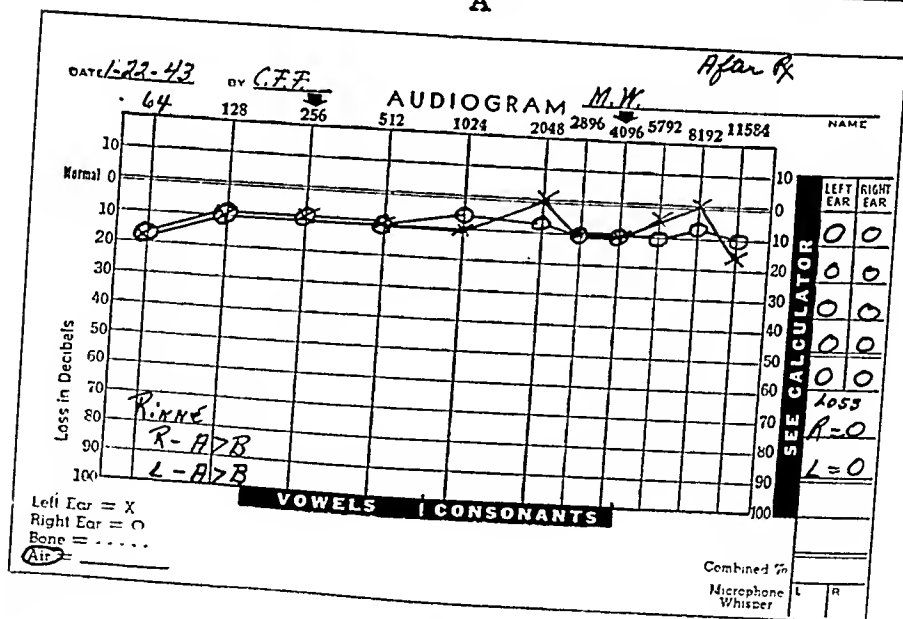
There are two other forms of *polymenorrhea* in which, although ovulation occurs at the more common interval of 14 days after flow, the succeeding period starts sooner than the 25th day One form, in which there is flowing about every 2 weeks, is due, not to displacement of the time of ovulation, but apparently to a delay in the immediately postovulatory secretion of sufficient progesterone by the corpus luteum to suppress the bleeding potential, which, as has been stated previously, is established in the endometrium by the estrogen

\* Flow recurring at intervals of less than 22 days is almost never cyclic for more than 3 or 4 months and is practically always a form of *aperiodomenorrhea* (discussed later)

a psychoneurotic with complaints of deafness that could never be evaluated. The remaining fourteen all showed improvement, and



A



B

Fig. 178.—Audiograms of another patient: A, before and B, after x-ray therapy. (Courtesy of Maico Acoustic Instrument Co., Minneapolis, Minn.)

twelve showed an excellent response as seen by accompanying table. Typical audiograms of two patients are shown in Figures 177 and 178.



without catamenia of, shall we say, at least 6 months. Accepting such a limitation of the diagnosis, we may consider that amenorrhea is always due to hypoestrinism, an amount of estrogen insufficient to cause proliferation of the endometrium and the establishment of the bleeding potential. I shall mention later the frequent cases where flow is absent, usually for less than 6 months, in which highly proliferated endometrium denotes prolonged secretion of appreciable amounts of estrogen. On the other hand, cases of amenorrhea for 6 months or more are probably always due to abnormally low secretion of estrogen, which is caused either by a failure of the ovarian follicles to respond to a normal or an increased amount of hormones from the anterior pituitary gland, or to lack of these substances because of pituitary dystrophy. Treatment, as described below, must be varied with due regard to different causes.

*Aperiodomenorrhea*—Other nonpathologic disorders of menstruation, which are not included in the categories mentioned—amenorrhea, oligo-, poly-, hypo- and hypermenorrhea—I have grouped under the diagnosis *aperiodo-*, or “immeasurable,” menorrhea. Even this is somewhat of a misnomer, as all patients thus afflicted do not flow with any degree of “monthly” regularity, but this is also the case with the terms “oligo-” and “polymenorrhea,” wherein the syllable “men,” meaning “monthly,” is also not invariably applicable. They are old and honored terms, however, so can safely engross this newcomer. *Aperiodomenorrhea* corresponds to the well known category of *dysfunctional flow*, *menometrorrhagia*, *metropathia haemorrhagica*, or *uterine insufficiency* of the older clinicians. In this condition, the bloody uterine discharge is immeasurable in incidence, duration, quantity and quality, it may occur every few days or weeks or be absent for months and last for days or weeks, even months. From time to time it may vary in amount from staining to excessive flow. Clots of various sizes may often be passed along with the fluid discharge.

*Aperiodomenorrhea* is due to failure of any one of many growing follicles to ovulate. Thus, no corpus luteum is formed, no progesterone is secreted. The bleeding potential is established in the endometrium by the estrogen of many active follicles, but is inhibited, not by progesterone, but only by this estrogen and then only so long as that critical change in the quantity or quality of the estrogen that will activate the bleeding mechanism fails to occur. Experimentally, in castrates, the sudden withdrawal of prolonged doses of estrogen is followed by bleeding from a proliferated endometrium. Likewise, if administration is continued indefinitely for many months, bleeding also occurs, even during the treatment. Without digressing into a discussion of the metabolism of estrogen and the control exerted on its degradation by progesterone,<sup>4</sup> we may infer from observation of ovaries in these cases, as well as from experimental work on monkeys,<sup>5</sup> that the absence of progesterone is the primary cause of the aperiod-

without hesitation the use of x-radiation because of the simplicity of treatment and because of its general availability. We feel that the response has been completely satisfactory, and that if radiation methods were more generally employed, many thousands of cases of permanent, partial or complete deafness could be obviated.

#### SUMMARY

The importance of the early recognition of conductive deafness due to excessive lymphoid tissue in the nasopharynx with blockage of the eustachian tubes has been emphasized.

The criteria for establishing the diagnosis have been elaborated, and the importance of careful audiometer tests has been discussed.

The treatment of this condition by means of roentgen therapy following primary adenoidectomy offers a simple and effective method of controlling most cases of conductive deafness in childhood. X-ray therapy should be available in all hospitals and should be more widely employed.

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or proliferative phase of the cycle when either hormone may unfortunately inhibit ovulation. Except by the use of pellets, treatment must be repeated during each cycle, and the cost of solutions for injection or, in the case of testosterone, of tablets, is prohibitive. Until more extensive studies of the use of pellets are made, this method of decreasing the effect of estrogen in the endometrium without inhibiting ovulation is denied to clinicians. Greenblatt<sup>9</sup> reported the helpful effect of pellets of testosterone propionate in cases of "functional menometrorrhagia" (what I call "dysfunctional aperiodomenorrhea," since ovulation is absent), as well as in some cases of functional hypermenorrhea. In discussing this paper, Salmon stated that he and Geist did not get such good results. There is hope that in the future we may decrease excessive estrogen stimulation of the endometrium by the male sex hormone. At present, other methods must be used to diminish excessive flow.

Years ago, the beneficial effect of injections of *chorionic hormone* (Antuitrin-S, Follutein, A P L, Korotrin, etc.) of the order of 1500 rat units, divided into about three doses, given daily, was recognized. Continued use has shown a beneficial effect in only about 30 per cent of the cases, and then only if the hormone is given during the flow. At present, I occasionally use it in functional hypermenorrhea, beginning on the second or third day of the profuse period. Theoretically, its influence is exerted on the bleeding potential. Its use is unsatisfactory, since the effect is limited to the single treated catamenia.

The second factor in bleeding is the amount of progesterone which conditions the metabolism of estrogen. Progesterone should not be used in functional hypermenorrhea. Although progesterone may inhibit expression of the bleeding potential, the latter may be enhanced by this hormone, so that withdrawal of it increases the flow. On the other hand, in hyper-aperiodomenorrhea, progesterone is the hormone of choice, as will be discussed later.

The other four factors in bleeding are the tissue response of the mucosa to estrogen stimulation, the reaction of the myometrium, the repair potential of the remaining mucosa, and the clotting power of the blood. In respect to these, we must depend on a normal basal metabolic rate, a normal blood picture, a normal position of the fundus, a normal diet of high vitamin content, and good hygiene.

I have found styptics and oxytocics of no avail. *Curettage* will relieve the condition sometimes for several months, more often for only one. *Radium* in doses of 1000 mg-hrs will stop the bleeding for many months, but should be used only in those cases of aperiodomenorrhea occurring so late in the thirties or in the forties that a prolonged or perhaps permanent suppression of ovulation, a not uncommon effect of such treatment, is no great hardship. I believe the same can be said of the only slightly less drastic but more popular use of *x-ray* in three divided doses, each of 50 roentgens. Even though he is unwarrantably not fearful of preventing ovulation, the careful clinician will

ingitis. Prompt recognition and treatment of foci of infection elsewhere in the body may prevent direct or hematogenous extension of the organisms to the meninges.

In the case of tuberculous meningitis, which still has a mortality of almost 100 per cent, the above measures are of paramount importance. Pending the development of specific remedies, on which a great deal of work is now being done, one can only hope that tuberculosis will be wiped out completely by public health measures.

More specific remedies are available to individuals intimately exposed to meningococcic infection. Even a small dose of one of the sulfonamides in common use, over a period of three or four days, may be justified. One dose of 2 gm. of sulfadiazine, for example, is usually sufficient to suppress meningococci in the nasopharynx of adult carriers. Institutions faced with an epidemic of meningococcic meningitis may wish to administer a small daily dose of a suitable sulfonamide such as sulfadiazine (approximately one-third to one-fourth the usual therapeutic dose) to its members, as long as the hazard exists.

#### DIAGNOSIS

Now that effective therapeutic tools are at hand, the early diagnosis of meningitis is of more than academic importance. The sooner these tools are brought to bear on the patient's illness, the better are his or her chances of survival with an intact central nervous system.

**Clinical Signs and Symptoms.**—The infrequency of meningitis in general practice serves to catch many physicians by surprise, even when the cardinal symptoms and signs, such as fever, headache, nausea, vomiting, stiff neck and back, and a positive Kernig, clearly present themselves. In infants it is too often the mother who first notices the bulging of the anterior fontanel. Inasmuch as meningitis is commonest in infancy it is worth while to emphasize that a bulging fontanel is a prime indication for a diagnostic lumbar puncture. Other evidence of meningitis may be equivocal or misleading. Often there is a history of a respiratory infection from which the infant is apparently recovering when he has a return of fever and becomes irritable or listless and refuses feedings or vomits repeatedly. The patient may be unresponsive. Convulsions and twitching of the face or extremities may set in. Stiffness of the neck and a positive Kernig sign may be elicited. On the other hand, the infant may be in a state of shock, with a subnormal temperature and a normal or low white blood count. The anterior fontanel may even be depressed and the patient limp and exhibit no stiffness of the neck. So uncertain and variable are the signs of meningitis in this age group that one should perform a lumbar puncture in every case when a reasonable *suspicion* of meningitis exists.

**Laboratory Examinations.**—After the history and physical examination, the timing of the procedures will depend on the judgment of the physician in charge. Usually the order is as follows:

cians and occasionally followed by improvement, consists of intramuscular injections of any of several preparations of *estradiol*, such as Progynon-B or DP (Schering), or of the ketohydroxyestrin, such as Theelin (Parke, Davis), in doses of about 5000 I U, given at weekly or biweekly intervals. In cases without vasomotor or emotional disturbances, others try weekly injections of *progesterone*, such as Proluton, (Schering) in doses of 5 mg given intramuscularly. Use in this manner of either estrogens or progesterone is unscientific, but, with the reservation made above regarding hypophyseal-inhibiting doses of the former, it is apparently quite harmless, and no one can say these hormones surely do not enhance the effectiveness of general health measures in those cases improved after the combined treatment.

Because the extracts from human pregnancy urine, from the anterior pituitary gland, and from pregnant mares' serum are all follicle-stimulating in varying degrees, injections of one or the other are still prescribed by some clinicians in the hope of evoking ovulation. I have seen no good results from such treatment, although I have experimented with many of these gonadotropes extensively during the last ten years.

Whereas to produce ovulation in amenorrhea and in aperiodomenorrhea is our main objective, to produce flow in the former and to regulate it in the latter is often quite satisfactory to the patient, especially if fertility is not an object. In aperiodomenorrhea, estrogen is present in variable amounts, and usually there is an established bleeding potential. When aperiodic flow is scanty, regularity and increase in amount may frequently be obtained by oral use of an estrogen for 21 days, e.g., 0.1 to 0.2 mg of diethylstilbestrol, or 0.1 mg of ethinyl estradiol (Schering). Withdrawal flow usually occurs within 10 days of cessation of dosage. This sequence may be kept up for many months, each 21-day period beginning with the onset of flow.

When the irregular flow is profuse, biopsy will show the endometrium to be in full proliferation. Secreted estrogen is already excessive so its therapeutic use is contraindicated. Likewise, the follicle-stimulating chorion or pituitary hormone should not be used, except, as has been mentioned above, when, during the flow, divided doses totaling about 1500 R U of chorionic hormone may be given for its theoretical hemostatic effect in the endometrium.

To regulate the flow in aperiodomenorrhea, progesterone is necessary. This is best given by 5 daily intramuscular injections, each of 5 mg. If these are started during the flow, it will almost invariably cease before the series is completed and recur in moderate amount within 10 days after the last injection. With this flow, subsequent to injection, the surface of the endometrium is shed, as in menstruation. This is what Albright<sup>13</sup> calls "medical D and C." After usually not more than 7 days, flow ceases, not to recur for several weeks. It is my

Organisms found in the original culture should be saved for possible future needs, such as tests of susceptibility to the chemotherapeutic agents employed.

*Spinal fluid sugar determinations* may be made in the chemical laboratory or by a rough estimation in the clinical laboratory. If 1, 2, 3, 4 and 5 drops of spinal fluid (from a 1 cc. pipette) are mixed respectively with the contents of five small test tubes, each containing 1 cc. of Benedict's qualitative reagent, and heated in boiling water for five minutes, the presence or absence of even a slight reduction at the end of this time indicates the presence of sugar. One or two drops of normal spinal fluid will usually cause some reduction. In purulent meningitis, the tubes may all remain blue as long as the infection is active. Normal spinal fluid usually contains 60 mg. or more of dextrose per 100 cc., provided the blood sugar level is normal.

Alexander has worked out a somewhat more accurate table, as follows:

Tube Number	Cerebro-spinal Fluid Added	Reduction of Benedict's Solution					
		+	0	0	0	0	0
1	0.05 cc.	+	0	0	0	0	0
2	0.1 cc.	+	+	0	0	0	0
3	0.15 cc.	+	+	+	0	0	0
4	0.2 cc.	+	+	+	+	0	0
5	0.25 cc.	+	+	+	+	+	0
Mg. of dextrose per 100 cc.		Over 50	40 to 50	30 to 40	20 to 30	10 to 20	10

*Virus infections of the meninges* are characterized by a tendency toward a lymphocytic cellular response in the cerebrospinal fluid, by a normal sugar content, negative smears and sterile cultures.

Whenever *tuberculous meningitis* is suspected, a tuberculin skin test, using a 1:10,000 dilution of Old Tuberculin or one comparable to this of another preparation, should be done at once. If this is negative, proceed with stronger dilutions, up to 0.1 cc. of 1:10 dilution Old Tuberculin. The spinal fluid may be examined by staining the centrifuged sediment or the web which forms for acid-fast bacilli enmeshed in the web. Painsstaking search on more than one occasion for a total of several hours is usually necessary. Culture and guinea pig inoculation with the centrifuged sediment may provide the only proof of tuberculous meningitis. Anxious relatives and friends press one for an early diagnosis.

### TREATMENT

**Supportive Measures.**—In fulminating or neglected infections, supportive measures may be life-saving and should at times take precedence over diagnostic and specific therapeutic measures. These include the administration of oxygen (tent, cone or nasal catheter) ether, other intravenous or subcutaneous sedatives to control convulsions, and above all, fluids. If there is evidence of dehydration or a history of persistent vomiting or inanition, intravenous fluids, such as 5 or 10 per cent dextrose in water (10 cc. per pound of body weight), followed by a hypodermoclysis of physiological saline solution (10 cc. per pound of body weight), are indicated. A continuous intravenous drip, to supply 10 cc. per pound per hour, may be advantageous in the more severe cases. When an infant shows evidence of acute cerebral edema, 10 to 20 cc. of 50 per cent dextrose solution intravenously may give temporary benefit. In milder infections, diagnostic and spe-

I have found that in cases of inexplicable infertility, associated with short cycles, an injection of 5 mg of Proluton (Schering) on the second and again on the fifth day after the estimated ovulation date, is often effective for the relief of barrenness. I believe it is useless to attempt to prolong the luteal phase except in such cases where fertility is the object. In others, our ignorance of means to regulate the complexities involved, especially as the misery, when its cause is explained to the patient, is minimal, renders unjustifiable the expense and the uncertainties of treatment.

### SUMMARY

1 Nonpathologic disorders of uterine flow may be divided into two categories *functional*, in which ovulation occurs, and *dysfunctional*, in which follicles, however closely they approach rupture, fail to complete this process. Diagnostics demands somewhat arbitrary limits to what we should call *normal* menstruation. The author's criteria are stated below.

2 The ovarian cycle of follicular growth, maturation of the ovum in at least one follicle, rupture of this follicle, corpus luteum formation and regression takes place ordinarily and normally in  $(28 \pm 2) \pm 2$  days. For months or years at a time, the cycle in most women remains as of  $v \pm 2$  days,  $v$  being any number within the limits  $(28 \pm 2)$ . Almost all women will have several cycles in the course of a year which extend beyond their pattern-range. When the cycles are habitually in the lower range of from 22 to 23 days in length, the condition is termed *polymenorrhea*. When menstruation frequently occurs at intervals of 21 days, ovulation is almost certain to have failed, and the condition is dysfunctional. When cycles are habitually of the longer variety and menstruation takes place at intervals longer than 32 days, even up to several weeks or months, the condition is called *oligomenorrhea*. Ovulation, in such cases, may occur as infrequently as only two or three times a year.

Flow occurring at fairly regular intervals but persisting for longer than 7 days, or requiring more than an average of four napkins per day, is called *hypermenorrhea*. If fairly cyclic flow lasts less than 4 days and requires less than an average of four napkins per day, it is called *hypomenorrhea*.

Functional disorders may also appear as combinations of these four main types, i.e., *oligo-hypomenorrhea*, *poly-hypermenorrhea*, and so forth. The significant characteristic of functional flow (always preceded by ovulation) is that it occurs in fairly constant cycles and that the bleeding is fairly similar in duration, quality and quantity in all the periods of flow.

3 The regularity and similarity of periods in normal menstruation, as also in functional disorders thereof, are due to the fact that the

The finding of a predominance of polymorphonuclears and reduced sugar in the initial spinal fluid specimen, even if organisms are not visible on smear, calls for sulfadiazine, pending an exact diagnosis of the causative agent.

The route of administration varies. In mild cases of meningitis it may be given orally, but it is probably wise to give at least the first two doses as the sodium salt either intravenously or subcutaneously (up to 5 per cent saline).

The first dose is 0.1 gm. per kilogram of body weight (or  $\frac{2}{3}$  grain per pound). This or a larger or smaller dose should be repeated in eight or twelve hours, *depending on the blood level*. Except in the case of meningococcal infections, which respond somewhat more readily than do the other forms, a blood level of at least 10 to 15 mg. per 100 cc. is desirable until the infection has subsided. Some clinics advocate even higher blood levels. As mentioned previously, an adequate intake of fluids is imperative in order to reduce the likelihood of renal complications.

As soon as the patient can swallow sulfadiazine and retain it, the drug may be given orally in divided doses ranging from 0.15 to 0.3 gm. per kilogram of body weight (1 to 2 grains per pound) per day, depending on the blood level desired.

*Penicillin*, when indicated, should be given intramuscularly for at least one week. It should be given intrathecally also for at least five days after the spinal fluid becomes sterile. When the response is slow or there is evidence of localized infection, a longer course should be adopted. Intrathecally it may be injected in concentrations of 1000 to 5000 units per cubic centimeter of physiologic saline, after spinal fluid has been withdrawn. In no case should a greater volume of fluid be injected than was withdrawn. The present trend is toward larger doses. Infants should probably receive 10,000 units twice a day and children and adults at least double this amount, in order to maintain a spinal fluid level of 0.05 Oxford units or more per cubic centimeter at all times.

A localized pocket of infection within the skull, when accessible, should be drained. Should the ventricles contain pus which cannot be drained off by lumbar or cisternal puncture, they may be irrigated with normal saline or Ringer's solution by means of suitable needles inserted through the lateral angles of the anterior fontanel or through burr holes. Penicillin, if indicated by the organism found, is then injected into the ventricles.

**Lumbar Puncture.**—So much importance is rightfully attached to the lumbar puncture that a summary of the indications for this procedure may be of value:

1. *Diagnostic.*—If the first spinal fluid obtained is normal but the condition still suggests the diagnosis of meningitis, the lumbar puncture should be repeated. If no fluid is obtained, after repeated trial at more



sity of the bleeding potential, and the promptness of the growth of new follicles, which will raise the concentration of estrogen up to a recurring inhibitory point

5 The treatment of menstrual disorders requires, first of all, meticulous attention to mental and physical hygiene. In addition, there are three more specific objectives: (a) to diminish the amount of flow, as in hypermenorrhea and in aperiodomenorrhea, (b) to cause ovulation, as in amenorrhea, marked oligomenorrhea, and aperiodomenorrhea, or, failing in this, at least to produce flow at acceptable intervals, (c) to prolong the life of the corpus luteum, as in some cases of polymenorrhea.

To accomplish these ends, we have, besides measures of general health, various hormones and stilbestrol derivatives

- (a) Extracts of the anterior pituitary gland of sheep, which are clinically follicle stimulating in varying degrees. They do not, except rarely and apparently accidentally, cause ovulation, although they do sometimes evoke slight flow.
- (b) Serum gonadotropes, derived from the serum of pregnant mares, which are similar in origin and effect to the anterior pituitary extracts.
- (c) Chorionic hormones, derived from the urine of pregnant women, which are mildly luteinizing and in addition have a slight inhibitory effect on the bleeding potential.
- (d) The estrogens, including stilbestrol derivatives, which stimulate the endometrium to proliferate and establish therein the bleeding potential. These hold in restraint this tendency to bleed, only to precipitate "withdrawal flow" when they themselves are withdrawn or catabolized. In small amounts, they may sometimes stimulate anterior pituitary gonadotropic activity.
- (e) Progesterone, which enhances but, more strongly than estrogen, inhibits the bleeding potential during its use, and promptly precipitates flow from the estrogen-conditioned endometrium when it is withdrawn.

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# ENDOCRINOLOGY. A SYNOPSIS OF NORMAL AND PATHOLOGIC PHYSIOLOGY, DIAGNOSTIC PROCEDURES, AND THERAPY

EDWARD C REIFENSTEIN, JR, MD, FACP\*

THE purpose of this paper is to summarize the high-lights of endocrinologic physiology, diagnosis and treatment. This review is deliberately dogmatic rather than controversial, it prefers to render less conspicuous the gaps in our factual knowledge by adhering to one organized system†, it attempts to be current but not complete. In brief, this outline is intended to supplement the section on endocrinology of textbooks of medicine and thus to assist the medical student, the intern and the nonendocrinologically trained physician in orienting himself to endocrine disturbances.

## GENERAL CONSIDERATIONS

**Hormone Interrelationships**—Available evidence indicates that the anterior portion of the pituitary gland is the hormone-regulating center of most of the other endocrine glands. The anterior pituitary is connected by nerve pathways via the hypothalamus with the central nervous system, and thus the hormonal system of the body is to some extent subject to nervous control.

The anterior pituitary exerts its influence on other glands by means of "tropic" hormones in response to which these "target" glands in turn produce "tissue-affecting" hormones. It is true, in general, that each tissue-affecting hormone inhibits or decreases the production of the tropic hormone that originally caused its production. Furthermore, the continued administration of an excess of any hormone (tropic or tissue-affecting) may result in the atrophy of the gland that is the endogenous source of this hormone. Likewise, a hormone-producing tumor will frequently be associated with an atrophy of the remaining

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From the Department of Medicine of the Harvard Medical School and the Medical Service of the Massachusetts General Hospital. Part of this material will appear as a section on "Endocrine Disturbances" in *Interns Handbook*, Syracuse University College of Medicine, 3rd ed, 1944, J. B. Lippincott Co., Philadelphia, publishers.

\* Research Fellow in Medicine, Harvard Medical School, Instructor in Medicine and Psychiatry, Syracuse University College of Medicine (on leave), Graduate Assistant in Medicine, Massachusetts General Hospital.

† The system is, in general, the author's interpretation of that formulated by Dr. Fuller Albright, and used by him and his associates (including the author) at the Massachusetts General Hospital. The original studies of these investigators have been supported by grants from the Josiah Macy, Jr. Foundation, the Rockefeller Foundation, and the Committee on Endocrinology of the National Research Council.

rection of delaying the formation of fibrinous adhesions. The exact dosage and interval has not been worked out, nor the possible combination of this method with oral dicoumarin or intravenous heparin. Their maximum effectiveness would appear to be early rather than late in the course of the disease.

4. *Observation of the Results of Treatment.*—Of course the clinical response of the patient is of great value but it may lag several days behind cerebrospinal fluid signs of improvement. These signs are: (1) fall of total protein and rise of sugar levels; (2) fall of white cell count and increase in relative number of lymphocytes; (3) disappearance of organisms from the smear; and (4) sterile cultures.

*Treatment of Particular Types of Meningitis.*—With these general outlines of treatment in mind and at the risk of being somewhat dogmatic, one may specify certain measures applicable to particular types of meningitis. Admittedly, therapy is in a state of flux and continuous improvement. What seems up-to-date today may soon need revising the light of later discoveries.

*Meningococcal Meningitis.*—This usually responds well to all the commoner sulfonamides. In fact, after adequate dosage of a sulfonamide, the spinal fluid is usually sterile within six to eight hours. If the response is delayed one should consider the possibility of sulfonamide resistance or a pocketing of pus within the subarachnoid space or inside the ventricles. The latter contingencies are commoner in infants. If the organism is sulfonamide-resistant, intrathecal or even intraventricular, penicillin may be substituted. Intravenous antiserum is very rarely necessary, except possibly in infants.

Five days after the spinal fluid becomes sterile and otherwise shows signs of improvement, sulfonamide therapy may be discontinued provided the general condition of the patient corroborates the laboratory findings. One should be particularly conservative in interpreting signs of improvement in infants who were sick more than three days before therapy was instituted or who responded slowly to treatment.

*Influenzal Meningitis.*—If the meningitis is caused by a respiratory strain of *Hemophilus influenzae* of relatively low virulence, spinal fluid drainage by lumbar puncture, possibly combined with sulfadiazine, is probably sufficient.

If the strain is type B, sulfadiazine and specific antiserum are indicated. Even in "mild" cases it seems wise to give antiserum without delay. While concentrated horse serum (Massachusetts State) intramuscularly in large doses (180 cc.) has cured children with meningitis quite promptly, at present intravenous rabbit serum (Squibb)\* is the method of choice. It has been standardized in terms of precipitable antibody nitrogen, each vial containing 25 mg.

Mild cases should receive at least 50 mg. and severe cases 150 mg.

\* Lederle may soon have a similar rabbit antiserum available commercially.

this is thought to be the mechanism of the gonadal underdevelopment which is part of Frohlich's syndrome. When the hypothalamic centers are deranged by an intracranial lesion, early release of the luteinizing hormone may occur with precocious puberty. Psychogenic disturbances may also prevent the nerve impulse to the release of luteinizing hormone, which results in females in amenorrhea of the type seen in anorexia nervosa (v infra). Other nerve pathways to the posterior pituitary regulate the release of the antidiuretic principle. When these pathways are interrupted this secretion is not produced, and the diuretic processes under the control of the anterior pituitary proceed unchecked with diabetes insipidus as the result. When the anterior pituitary is destroyed as well as the nerves to the posterior lobe, diabetes insipidus does not occur.

**Anterior Pituitary**—The anterior pituitary gland is composed of at least three types of cells: the acidophil (A), the basophil (B), and the chromophobe (C). Only the first two of these are known to produce hormones, which are chiefly "tropic."

The hormones produced by the acidophil cells include (a) somatotrophic or *growth hormone*, (b) thyrotrophic or *thyroid-stimulating hormone*, (c) *adrenal corticotrophic hormone*, (d) "*diabetogenic*" hormone, and (e) *lactogenic hormone*. There is some incomplete evidence that there may be tropic hormones to the pancreas, the parathyroids, and the adrenal medulla. One of the gonadotropic hormones (the luteinizing hormone) may be produced by the A cells, but the evidence is insufficient so that for the present it is included in the group produced by the B cells.

The hormones produced by the basophil cells are all gonadotropic: (a) *follicle-stimulating hormone*, (b) *lutemizing hormone*, and (c) *luteotrophin*. This latter may be the same hormone as the lactogenic hormone (and hence be produced by the A cells). Nerve pathways from the hypothalamus seem to be connected chiefly with the production of luteinizing hormones; some lesions in the hypothalamus cause an increase and others a decrease in this hormone.

The functions of the tropic hormones of the A group are of theoretical interest only, since there are no preparations of any of these (except possibly the lactogenic hormone) which can be recommended for use at the present time because of the danger of "antihormone" formation (v supra). We may summarize briefly the functions of this group as follows: (a) the somatotrophic hormone promotes growth of tissues by stimulating the growth of cartilage and by inducing protein tissue anabolism, (b) the thyrotrophic hormone is the thyroid-stimulating hormone, (c) the adrenal corticotrophic hormone stimulates the adrenal cortex to produce one or more of the hormones which have to do with electrolyte regulation, gluconeogenesis (protein catabolism) and protein anabolism, (d) the "diabetogenic" hormone reduces the effectiveness of and hence temporarily increases the production of

lated and the donor whose fresh defibrinated blood exhibits optimal phagocytosis is selected.

*Staphylococcal Meningitis.*—Penicillin is now the drug of choice in meningitis due to the *Staphylococcus aureus*, although cures have been reported following the use of sulfonamides, particularly sulfathiazole. Large doses should be given early in the course of treatment. Abscesses should be drained.

*Meningitis Due to Escherichia Coli.*—To date, all but three patients suffering from this type of meningitis at the Infants' and Children's Hospitals have died. There are reports in the literature (*Lancet*, 248: 176 [Feb. 10] 1945) of adults who were successfully treated with 30 gm. of urea and 2 gm. of sulfadiazine by mouth every four hours.

It is possible that meningitis caused by some of the other gram-negative bacilli would respond to this treatment. Transfusions of blood may be worth while.

*Conclusion.*—In conclusion, one should emphasize that early recognition of meningitis is of extreme importance and time and thought spent in the first few days of treatment usually pay big dividends. One should not be discouraged by seemingly hopeless situations or slow response to treatment. Adequate citizens capable of useful and happy existence may be the reward of perseverance.

of the uterus during the time that it is under the influence of estrogens, but not during the period when it is responding to progesterone. Pitressin exerts an antidiuretic action by inducing tubular reabsorption in the kidney, a diuretic effect is apparently maintained by the anterior pituitary. Pitressin also induces peripheral vasoconstriction and stimulates smooth muscle. A hormone arising from the intermediate lobe causes a dispersion of black pigment granules in the epidermal melanophores.

**Ovary**—The relationship of the pituitary gonadotropic hormones and the ovary has already been mentioned. Under the influence of these hormones, the follicle produces *alpha estradiol*, and the corpus luteum produces *progesterone*.

The former has the following effects: (1) it inhibits the follicle-stimulating hormone, (2) it stimulates the production of luteinizing hormone, (3) it neutralizes some of the effects of androgen (such as testosterone) in the tissues, (4) it causes growth, thickening and cornification of the vaginal mucosa with deposition of glycogen and formation of a more acid secretion, (5) it causes growth of the myometrium and proliferation of the endometrium of the uterus with a growth of the glands (if continued long enough it produces marked hyperplasia), (6) it increases uterine motility by augmenting the action of pitocin, (7) it induces development of the nipples and the mammary glands (growth of the ducts and possibly of the alveoli), (8) it inhibits the lactogenic hormone, (9) it stimulates the osteoblasts, (10) it produces a moderate, transitory increase of protein tissue formation, (11) it maintains the skin and mucous membranes, (12) it tends to lower the serum phosphorus, (13) it tends to decrease the gland cells and increase the stroma of the prostate, perhaps through effect (3), (14) it causes atrophy of the testicular tubules, and (15) it decreases libido. If continued long enough in the female, it will prevent ovulation through effect (1). Lack of estrogen will cause the opposite of effects (1) through (9). Withdrawal of or sharp reduction in the amount of estrogen, therefore, tends to be followed by uterine bleeding. It has been suggested, but not proved, that in *susceptible* persons huge doses of estrogens may induce new growth formation.

Progesterone has the following effects: (1) it inhibits the luteinizing hormone, (2) it seems to stimulate the production of follicle-stimulating hormone, (3) it converts the endometrial glands into a secretory state and prepares the endometrium for implantation of the ovum, (4) it decreases uterine motility by inhibiting the action of pitocin, (5) it maintains the functional activity of the placental, (6) it promotes the development of the acinar (secretory) tissue of the breast, (7) it affects the renal tubules so that water, sodium and chloride are conserved and potassium is excreted, and (8) it is thought to facilitate the metabolism of *alpha estradiol* so that the urinary breakdown

arthritis, but it is important to keep in mind others such as Paget's disease, neuritis from avitaminosis, osteomalacia, pernicious anemia with spinal cord changes, hyperparathyroidism, Parkinson's disease associated with muscle rigidity rather than tremor, carcinoma, spinal cord tumor, ruptured intervertebral disk, various conditions causing edema such as nephritis, hypoproteinemia, myxedema, scleroderma, sclerodactylia and dermatomyositis.

### CLASSIFICATION

The twilight group of diseases associated with joint pains which are called "arthralgia" because we do not yet know that they represent true arthritis, might include postural joint strain, thyroid deficiency, menopausal state or ovarian deficiency, vitamin B complex deficiency, psychologic states and emotional conflicts, and physical fatigue.

A convenient classification\* of cases of true arthritis follows:

#### I. ARTHRITIS OF KNOWN ETIOLOGY

##### A. Traumatic arthritis

##### B. Infectious arthritis

1. Associated with diseases due to known specific organisms such as the gonococcus, staphylococcus, streptococcus, pneumococcus, meningococcus, tubercle bacillus, typhoid bacillus, *Treponema pallidum*, the brucella group, *Bacillus dysenteriae*, the organism of lymphopathia venereum, etc.
2. Associated with diseases probably infectious, such as acute disseminated lupus erythematosus, erythema nodosum, ulcerative colitis and periarteritis nodosum.

##### C. Metabolic arthritis; gout, scurvy, ochronosis

##### D. Allergic arthritis; serum sickness

##### E. Neuropathic arthritis; tabes dorsalis (Charcot's joint), syringomyelia, leprosy, yaws, hemiplegia, peripheral nerve lesions.

#### II. ARTHRITIS OF UNKNOWN ETIOLOGY

##### A. Rheumatoid arthritis (atrophic, proliferative, or chronic infectious arthritis). This also includes Still's disease, rheumatoid spondylitis (Marie-Strümpell, von Bechterew's types) and psoriatic arthritis

##### B. Degenerative joint disease (degenerative arthritis, hypertrophic arthritis, osteoarthritis, and German arthritis deformans)

##### C. Rheumatic fever

#### III. MISCELLANEOUS TYPES OF ARTHRITIS

Fibrositis, hemophilia, purpura, pulmonary osteoarthropathy, intermittent hydroarthrosis, hysteria

It is frequently stated that one should make the diagnosis of arthritis early, before there is clear-cut clinical or roentgenologic evidence of damage to the essential joint structures. This is a difficult thing to do, and even physicians who are spending most of their time seeing arthritic patients find it so. They would even disagree as to the nature of the disease in many early cases. It is for this reason that in early cases it is important to take the matter seriously and in taking the his-

\* Cabot, R. C. and Adams, F. D.: *Physical Diagnosis*. Baltimore, Williams & Wilkins Co., 1942.



thymus glands These various hormones of the adrenal cortex, particularly desoxycorticosterone and corticosterone, are produced in part by the stimulus of the anterior pituitary adrenal corticotrophic hormone As mentioned before, the androgenic hormone may be produced by the stimulation of the gonadotropic luteinizing hormone

Any damaging event excites the "alarm reaction"<sup>3</sup> in which the adrenals enlarge, and produce more corticosterone which thereby (a) increases systemic protein tissue catabolism (perhaps to supply the damaged area with energy [carbohydrate] and protein tissue raw materials) and (b) induces thymus involution (perhaps to furnish nuclear material) Persons dying after illness have the changes in the adrenal and thymus of the alarm reaction, those dying suddenly have normal-sized adrenal and thymus glands (the latter originally mistakenly called hyperplasia) Thus, the so-called "status lymphaticus" is not a disease but the normal physiologic state of one who dies too quickly to develop an "alarm reaction" A definite constitution predisposed to sudden death probably does not exist

**Adrenal Medulla**—The adrenal medulla produces *epinephrine*, which causes, in general, the effects of stimulation of the sympathetic nervous system (sympathomimetic effects) It constricts the peripheral blood vessels thus raising the blood pressure, dilates the coronary arteries, increases the blood sugar and blood lactic acid by accelerating the rate of enzymatic breakdown of glycogen in the liver and muscle and increases the basal metabolic rate The evidence for a pituitary "tropic" hormone affecting the adrenal medulla is meager

**Thyroid**<sup>4</sup>—The thyrotropic or thyroid-stimulating hormone of the anterior pituitary stimulates the thyroid gland to produce its hormone The thyroid hormone has the following effects (1) it raises the basal metabolism, (2) it is necessary for normal growth, (3) it maintains the normal excretion of water, salts and colloids, (4) it tends to reduce the level of the blood lipids, particularly cholesterol, (5) it decreases liver glycogen, (6) it increases protein catabolism, (7) it is necessary for normal emotional responsiveness, cerebral activity, sensory acuity, alertness, vasomotor and peristaltic activity, (8) it increases creatinuria, (9) it increases the irritability of the cardiac muscle, (10) it increases the tolerance to some types of drugs, particularly morphine and digitalis, (11) it increases the rate of absorption from the gastrointestinal tract, (12) it inhibits the production of thyroid-stimulating hormone, (13) it causes enlargement of the adrenal cortex, (14) it increases the sensitivity of the organism to epinephrine, and (15) it increases the production of gonadal hormones Lack of the thyroid hormone causes the reverse of most of these effects In the absence of adequate iodine, normal thyroid hormone is not produced

**Parathyroid**<sup>5</sup>—The parathyroid hormone regulates the calcium and phosphorus metabolism The chief effect of the hormone is to increase the excretion of phosphorus in the urine, this in turn decreases the

complete nutrition and the glandular imbalance of the menopause.<sup>3</sup> As we have watched patients with these conditions, we have come to the conclusion that these deficiency states lead to increased vulnerability of tissues so that the trauma of ordinary use—trauma to joint tissues and to muscles and tendons—produces pain and various degrees of disability. We became convinced of this with regard to the menopausal group by an unusual experience with one patient.

The patient, who was at the physiologic menopause, had many menopausal symptoms and was hospitalized because of the extreme pain in most of her joints. This was accompanied by hypertrophic arthritis in the fingers. However, it became quite clear that the tissues all over the body were abnormally sensitive. Pressure over the forearm would make her cringe. Taking the blood pressure caused pain. Abdominal examination was unsatisfactory and caused discomfort, and pelvic examination was impossible for the same reason. Three weeks later, following therapy with large doses of estrin, most of this sensitivity had disappeared, and all examinations could be made without distress.

We have seen instances somewhat less striking than this in many patients at the menopause. We have seen nothing as dramatic in cases of incomplete nutrition, but certain responses have suggested that incomplete nutrition may well be responsible for somewhat similar symptoms.

Many physicians apparently are unaware of the prevalence of incomplete nutrition in patients with joint disturbances. It is pointed out that most people eat a satisfactory diet. However, if one watches tongues, skin and eyes for evidence of incomplete nutrition, one finds a great many more cases of avitaminosis in patients with seemingly adequate diet than one would believe possible. We find only a few instances of an *incomplete intake* of the various protective foods. Among women the most common foods left out are milk, eggs and meat (or protein foods). This last is more common of late, and we have observed quite a number of persons with the total protein of the blood low and some edema of the ankles, which with the history of incomplete intake of protein would definitely indicate hypoproteinemia. A certain number of people have an *increased requirement* for protective foods. The requirement is definitely increased by long hours of work and short hours of sleep. It is increased by alcohol, sugar, hyperthyroidism, pregnancy, and infections.

The most common cause of incomplete nutrition, however, seems to be hyperperistalsis resulting in *incomplete absorption* of food. The most dramatic cases are seen in patients with diverticulosis or an irritable colon. They come with a history of having had three to five bowel movements a day over a long period of time, or intermittent attacks of this hyperperistalsis. Such patients usually show very definite evidence of B avitaminosis in the tongue and skin, but in all probability there is a deficiency of all known vitamins, plus a probable deficiency of other food factors that we do not yet know. Less striking, but

pituitary lactogenic hormone, prolactin, has a secretagogue action and induces the release of milk

**Placenta**—The placenta produces several hormones (1) *anterior-pituitary-like hormone* (A P L), (2) *progesterone*, and (3) *estrogen*. A P L is a chorionic gonadotropin, but has many similarities to the luteinizing hormone of the anterior pituitary and induces most of its effects (v supra). During the first few days of pregnancy, A P L maintains the corpus luteum of pregnancy, this is spoken of as the period of "pituitary adoption." Hypophysectomy after this time does not interrupt pregnancy in animals. About the second or third month, the placenta produces enough progesterone and estrogen so that the ovary may be removed in the human without interrupting pregnancy. This is called the period of "ovarian adoption." The progesterone and estrogen seem to be identical with those produced by the ovary (v supra). Neoplasms of chorionic tissue, such as chorionepithelioma, in either the male or the female produce a high titer of A.P.L.

#### ENDOCRINE DIAGNOSTIC PROCEDURES

Endocrine disturbances should be considered merely as problems in internal medicine. The same thorough survey of these cases should be made as in any other field of medicine. The program for studying endocrine problems includes (1) complete history, (2) thorough physical examination, (3) routine diagnostic procedures and (4) special endocrine diagnostic procedures. A description of some of the latter follows.

**Blood**—Except as otherwise indicated, the normal values and the methods of collection are standard and generally known. The major abnormalities suggesting endocrine disease are cited below.

- 1 *Calcium* Elevated in hyperparathyroidism, decreased in hypoparathyroidism (Syringes and tubes for collecting blood for this determination should be rinsed with calcium-free distilled water and dried in air or with low calcium filter paper.)
- 2 *Phosphorus*\* Elevated in acromegaly,<sup>7</sup> hypoparathyroidism, Addisonian crisis, and adequately growing children, decreased in hyperparathyroidism.
- 3 *Alkaline Phosphatase*\* Elevated in hyperparathyroidism with bone disease, and carcinoma of the prostate with bone metastases. Normal level 3 to 5 Bodansky Units is so low that decreased levels cannot be detected.
- 4 *Acid Phosphatase*\* Usually elevated in carcinoma of the prostate, but normal level does not exclude this condition.<sup>8</sup> Normal level under 4 G units.
- 5 *Cholesterol* Elevated in hypothyroidism and diabetes, decreased in hyperthyroidism.
- 6 *Sodium* Decreased in adrenal cortical insufficiency (Addison's disease).
- 7 *Potassium* Increased in adrenal cortical insufficiency (Addison's disease).
- 8 *Chloride* Decreased in adrenal cortical insufficiency (Addison's disease), also at times decreased in Cushing's syndrome.

\* Collect blood for this determination the same as for calcium.

thinking of the gastrointestinal tract as a factory for the processing and absorption of food, and one must encourage the patient to have only one formed movement every day or every other day. Often it is quite a psychological hurdle to convince such patients that dire things will not happen if the bowels are kept really slow acting. One has to plan the diet so that there will be a proper amount of green vegetables and fruit in a form that can be tolerated. Such patients often have to give up indefinitely raw vegetables such as salads and celery, and rough foods like corn and sometimes spinach. Bismuth or kaolin and paregoric, to be taken before going to bed each night, may be of value at times, when only mild soothing of the bowel is needed. Sedatives sometimes help such hyperperistalsis. The presence of hyperthyroidism needs to be ruled out, and emotional conflicts resolved, if present. Supplementary vitamins of all types would seem to be indicated in very large doses. Until one is convinced that absorption is complete, especially in older persons, parenteral therapy is often indicated. In such cases we give very large doses of vitamins by mouth, using the multiple vitamin preparations and 2 cc. of B complex with a liver base intramuscularly twice a week. As these persons are sick, it is important to treat them as such, with extra quotas of rest which of course cut down the nutritional requirements.

6. *Menopausal Arthralgia*.<sup>3</sup>—This type of joint pain should be easily recognized if sought. The diagnosis is clear when the arthritis occurs within weeks or a few years after destruction or removal of the ovaries, and when definite symptoms of the menopause are present. It is usually possible to detect this type of arthralgia when it occurs at the physiologic menopause. It may be easily overlooked when other contributing factors to the patient's poor health are present, such as those previously mentioned. It is apt to be out of mind entirely when it occurs superimposed on a definite type of arthritis such as the hypertrophic type or the rheumatoid type. Its importance sometimes in such conditions cannot be overstated.

An example of this occurred in a nurse of 56 who came to the hospital severely crippled with rheumatoid arthritis of ten years' duration. In addition to the permanent joint changes there was marked pain in the left hip requiring her to be put into a plaster shell. Improvement seemed to stop after a few weeks, and the whole history was again searched for leads suggesting some specific etiology. Though she had denied any menopausal symptoms, we had suspected that her sleeplessness, her depression and nervous tension, and her dissatisfaction with the temperature of the room at night, however we kept it, represented menopausal symptoms. Further questioning brought out other symptoms, especially change in the patient and started her toward improvement. Instead of being bedfast in the last few years she has become increasingly active, and though we do not attribute this to the sex hormone alone, we feel that it contributed to her improvement in no small measure because improvement in the joints as well as in her general health occurred within a few weeks after she took this material.

*insulin should be reduced to one-half or one-third of the calculated dose to minimize serious reactions* In cases with insulin resistance, further evidence can be obtained by repeating the test with twice the calculated dose of insulin

4 In the *glucose-insulin tolerance test* the amount of glucose that is given in the glucose tolerance test and the amount of insulin that is given in the insulin tolerance test are administered simultaneously. Blood samples are taken at 0,  $\frac{1}{2}$ , 1, 2, 3 and sometimes 4 hours. The normal level should remain approximately flat, "insulin resistance" is indicated by a curve that approximates the glucose tolerance test, "insulin sensitivity" is indicated by a curve that approximates the insulin tolerance test

Urine—Two types of urine specimens are used for hormone assays (1) the first morning specimen, and (2) the 'overnight specimen. Fluids should be restricted for 12 hours before a morning specimen is collected so that the specific gravity of the specimen is at least 1.015. To collect an overnight specimen the patient voids and discards at bedtime, but the time is noted, he then voids and saves the complete specimen obtained on arising in the morning, the time is noted again. Any urine voided during the night is included in the specimen.

1 *APL Test*—The excretion of anterior-pituitary-like substances (APL) in the urine is increased in pregnancy, chorionepithelioma, hydatidiform mole, and testicular teratoma. These substances in suitable doses will cause corpora haemorrhagica or fresh corpora lutea in infantile mice (Aschheim-Zondek test) or in immature female rabbits (Friedman test). A morning specimen is required.

2 *FSH Test*—The excretion of the follicle-stimulating hormone (FSH) of the pituitary is increased in the menopause, castration, primary hypogonadism, and the syndromes of ovarian dwarfism,<sup>10</sup> functional prepubertal castration,<sup>11</sup> and gynecomastia and small testes.<sup>12</sup> The excretion is decreased in panhypopituitarism,<sup>13</sup> pituitary amenorrhea,<sup>14</sup> Frohlich's syndrome, some cases of Cushing's syndrome (hyperadrenocorticism), and in patients with arrhenoblastoma, granulosa and theca cell tumors, some cases of hypospermatogenesis, and probably in those with Leydig cell tumors. In other gonadal syndromes such as metropathia haemorrhagica, dysmenorrhea, large-pale-ovary syndrome, "hypothalamic" amenorrhea and hypoleydigism the excretion is normal. The FSH test depends on the principle that this hormone in suitable doses will increase the size of the uterus of immature female mice by stimulating the mouse ovary to produce estrin. An overnight specimen is required to test for an excess and one representing from 8 to 16 hours is needed to test for too little. Normal values are in the range of 13 to 52 mouse units per 24 hours.<sup>15</sup>

3 *17-Ketosteroid Test*—Some urinary excretory products of the "sex" hormones of the adrenal cortex and of the testis hormone (testosterone) contain a steroid nucleus with a ketone group on the 17th

or if improvement is so slow as to be unconvincing, she is likely to lose confidence in the whole program.

Not infrequently there is evidence of incomplete nutrition as well as a menopausal problem in a patient, and one cannot help but speculate as to whether patients with severe menopausal symptoms and those with symptoms that continue for many years may not lack certain chemical building stones necessary for the glandular readjustment. It would seem basically important in such patients to make sure that any nutritional deficiency is corrected. Surely the menopause should be a relatively normal stage of life and not attended by as much difficulty as we often see. It is our impression that the patients who receive supplementary vitamins as indicated make the best response and require estrin treatment for a shorter length of time than when vitamins are not used, and we suspect that some of these patients might do well with simply the nutritional approach alone.

#### THE ARTHRITIDES

Much of what we have noted in respect to arthralgia applies equally to arthritis, for the various conditions we have mentioned are commonly found in persons with chronic arthritis, but one of the first important things to do in studying a patient is to determine if possible the type of arthritis with which one is dealing, to the end that where the cause is known, the treatment may be precise. Traumatic arthritis is usually clear-cut and the chronic microtrauma of poor posture is usually easily recognizable. Sometimes only trauma is present. It is a contributing factor in practically all other types of arthritis. The possibility of the arthritis being due to infection will naturally be kept in mind and, so far as possible, infection will be treated specifically by modern drugs or removed surgically. Space does not permit the inclusion in this article of a discussion of gout or allergic arthritis or the neuropathic group.

It is especially in the two main types of chronic arthritis, namely rheumatoid and hypertrophic arthritis (or degenerative joint disease), that what we have noted in the preceding paragraphs seems to apply. We still do not know the cause of these two types of arthritis. The rheumatoid type is still generally thought to be due to infection, while degenerative joint disease, or hypertrophic arthritis, is thought to be due to the wearing out of the joints. Descriptions of the clinical pattern and the pathological findings in these two types can be found in textbooks. The fact that there are so many mixed types raises again the old question as to whether both types may not have common factors in their etiology, with the character and intensity of the irritant, its duration, plus the presence and absence of the trauma of use resulting in the pathological findings which we use to distinguish the two types of joint disease. Joint tissues can respond to various irritants or traumas in only a limited number of ways, and one could offer con-

8 *Urine Concentration Tests for Addison's Disease*—The ability to produce diuresis and to concentrate chloride and urea are tested by the Robinson, Power, Kepler modification<sup>17</sup> of the Cutler, Power, Wilder procedures. The technic is as follows. The patient takes no food or drink after 6 00 P M, voids at 10 30 P M, and the urine is discarded. The volume of the night urine from 10 30 P M until 7 30 A M is recorded, the sample being saved in case the chemical examination becomes necessary. The patient then voids at hourly intervals from 7 30 A M to 12 30 P M, merely the volumes being recorded. At 8 30 A M he is given 20 cc water per kilogram of body weight, to be taken within 45 minutes. It is the diuresis thereby induced that is the criterion of renal function and hence of adrenal cortex integrity. If the volume of any 1-hour fraction exceeds the night volume (9 hours), adrenal insufficiency is eliminated. If such adequate diuresis does not occur, blood should be drawn at the close of the test for determination of urea and chloride in the plasma. In this case the urine of the 9-hour night specimen is also analyzed for chloride and urea, and the results are calculated by a formula as follows:

$$A = \frac{\text{Urea in urine}}{\text{Urea in plasma}} \times \frac{\text{Chloride in plasma}}{\text{Chloride in urine}} \times \frac{\text{Largest vol of urine (1 hr)}}{\text{Vol of night urine (9 hr)}}$$

This value, A, is 30 or greater in patients without Addison's disease, but when it is 25 or less Addison's disease is usually present. The exceptions are patients with nephritis.

9 *Urine Concentration Tests for Diabetes Insipidus*—The patient takes no food or water after 6 00 P M, voids at 10 30 P M, and the urine is discarded. The night urine is collected at 7 30 A M, and the specific gravity is recorded. If this specific gravity is less than 1 020, pitressin in a dose of 0 5 to 1 0 cc is administered subcutaneously at 7 30 A M. The patient voids at hourly intervals thereafter for 3 hours, and the specific gravity is recorded. The restriction in fluids overnight induces in diabetes insipidus a characteristic syndrome of intense thirst, headache, fatigue, loss of weight, hypothermia, tachycardia and prostration, in spite of this the first morning specimen has a specific gravity of less than 1 006. The administration of the pitressin ameliorates the symptoms, and raises the specific gravity of the urine. In patients without diabetes insipidus the restriction of fluids produces negligible symptoms, and a urine with a specific gravity of more than 1 020 unless organic renal disease is present. Pitressin has no effect on the low specific gravity urine excreted because of organic renal disease.

**Basal Metabolic Rate**—The amount of oxygen consumed per minute by the subject under basal conditions is compared with the normal standard for the age, sex and body surface area of the subject. To insure a basal rate, the subject at the time of testing must (a) have had nothing to eat or drink except water for at least 12 hours, (b) have had a minimum of physical exertion for at least an hour, (c) be

many cases given this diagnosis present contradictory pictures one wonders whether other types of arthritis might not be included in this classification. In the circumstances it seems important in an individual case to have an open mind and feel one's way along, doing everything possible to build up the general health of the patient, and not relying on any one drug.

We have used gold therapy in perhaps 150 cases of rheumatoid arthritis. We are not enthusiastic about its value when it is used alone, and we still are afraid of gold, but we could point to numerous cases that did not respond to treatment until gold was used, and that appeared to be completely arrested following its employment. In using gold salts we generally give 10 mg. of a product such as solganol-B in oil from two to four doses at intervals of four to five days; then two to four doses of 25 mg. at weekly intervals; then maximum doses of 50 mg. once a week. We have continued this program until the patient's symptoms were markedly lessened, or until a total of 1 gm. of the salt has been given. If the patient's symptoms are greatly improved at any point in the treatment we increase the interval between doses to two, three or four weeks. Even when the arthritis seems to be under good control, we continue to give 50 to 100 mg. once a month for six months more.

We are conscious that the doses advised are smaller than those ordinarily used. Our results are probably less spectacular, therefore, than those of many others who report on the use of gold salts. It should be stated, however, that even with these smaller doses we have seen enough patients with prolonged and disfiguring dermatitis, with prolonged periods of albuminuria, or with falls of blood platelets below 200,000 per cc. to make us eager to avoid the more frequent toxic reactions that all agree can result from the larger doses. We prefer, first, to use every other means possible to help our rheumatoid arthritic patients, then if these means fail to use as little gold as possible, and finally if gold is used to stop it as soon as possible.

During the process of treatment it is particularly important to educate the patient in the art of living, and then to keep in touch with him after he is considered to be well. Crippled joints can be reconstructed to an extraordinary extent by the orthopedic surgeons, and where it is perfectly clear that the arthritic process is quiescent as noted by the absence of any new joint disturbance, the absence of morning stiffness, and the absence of an elevated sedimentation index, one can expect operative procedures on joints to be remedial without the development of stiff joints from the operation.

**Degenerative Joint Disease and Hypertrophic Arthritis (Osteoarthritis).**—Trauma is considered to be the major factor in the development of hypertrophic arthritis. Trauma is unquestionably an important factor in all joint diseases and needs to be so considered, yet careful studies of patients seem to indicate that an  $x$  factor must be added to the



The cervical os is grasped with a tenaculum, and painted with 0.5 strength iodine solution. Then a uterine sound is inserted. There is usually a short cramp as the internal sphincter is passed. The sound is then removed and the biopsy curette (such as Meig's) is inserted and the specimen obtained. This is placed in a suitably labeled bottle of Zenker's solution and sent to the pathology laboratory.

**2 Testicular**—This also should be attempted only by a competent surgeon. The patient should be instructed to provide himself with a suitable suspensory prior to the operation. Following the operative procedure the specimen should be placed in a suitably labeled bottle of fixative solution and sent to the pathology laboratory.

**Spermatozoa Count**—The specimen should be counted as soon as possible, and never longer than 2 hours after collection. The equipment required includes a blood counting chamber, a white blood cell pipette, and a solution of 1 per cent formaldehyde in 5 per cent sodium bicarbonate. The procedure is as follows: draw the semen up to the 0.5 mark on the pipette and dilute to the 11 mark with the solution. Shake for 5 minutes. Load the counting chamber as for a blood count. Let settle for 1 to 2 minutes. Count the red blood cell squares, one in each corner, and one in the middle, a total of 5 squares. Add 6 zeros to obtain the count of spermatozoa in one cubic centimeter. Normal level is above 60,000,000. A hanging-drop preparation should be examined also to determine the motility of the sperm. Collection of the ejaculate in a bottle affords the only satisfactory specimen.

**Mensuration**—The body weight, the standing height, and the span should be carefully determined in every case.

**Roentgen Ray Examination**—The following studies are of aid in diagnosing endocrine disease:

- 1 **Bone Age** Delayed in panhypopituitarism, in other cases of pituitary underfunction, hypothyroidism and in hypogonadism, increased in precocious puberty. The normal osseous development has been tabulated by Engelbach.<sup>20</sup>
- 2 **Skull Plates** Sella turcica changes in pituitary tumors, calcification in suprasellar cysts, osteoporosis in Cushing's syndrome, decalcification in hyperparathyroidism,<sup>6</sup> calcification in choroid plexus<sup>21</sup> and density of bone in hypoparathyroidism.
- 3 **Spine** Wide thoracic vertebrae in acromegaly, crushed, wedged, or "cod-fish" vertebrae in osteoporosis of postmenopausal,<sup>22</sup> senile or Cushing's syndromes,<sup>23</sup> "epiphysitis" with long-standing gonadal deficiency, increased density with metastases from carcinoma of prostate (may simulate Paget's disease).
- 4 **Teeth** Absence of lamina dura in hyperparathyroidism, "blunted roots" in hypoparathyroidism.<sup>24</sup>
- 5 **Phalanges** Terminal tufting in acromegaly.
- 6 **Kidney, Ureter, Bladder Plate** Renal calculi in hyperparathyroidism,<sup>25</sup> Cushing's syndrome, osteoporosis, displacement of kidney with adrenal tumor or hyperplasia, decreased density of bony pelvis in osteoporosis, increased density with metastases from carcinoma of prostate.

her improvement was due to the fact that she was willing over a long period of time to go to bed whenever she had pain, and to stay there until the pain passed. At first she was in bed a great many weeks. As the years passed, she would occasionally have to go to bed for only a few days at a time. She had learned that her damaged hip, if used beyond a certain point, would always give pain, but she had become very alert to recognizing stiffness after sitting as the first evidence of increased joint irritation. She would then spend a few days in bed, and would be able to be active with restrictions for some weeks before having to do the same thing again.

Patients without the marked disability present in this patient will often recover almost normal walking capacity under such a program, because the reserves of the joint seem to be as great as the reserves in other organs and a patient can be fairly active in spite of a good deal of joint damage. This attitude is similar to that taken in heart disease, in which the patient has to build up his cardiac reserve and then learn to live within it. We have other patients who had had similar records. Some have taken thyroid or estrin; others have needed to watch their diet or their bowels carefully and take supplementary vitamins, but they all have kept off their feet when there was pain or stiffness. Patients with hypertrophic arthritis often tend to be overweight while those with rheumatoid arthritis tend to be underweight. It seems important to put weight onto the latter and to take weight off of the former. However, we are convinced that the removal of weight by dieting must be done slowly, carefully, and with great stress on protective foods and supplementary vitamins. The removal of weight seems to help definitely the nutrition in joints and it also serves to remove in part the trauma that overweight puts onto already damaged weight-bearing joints. Thus again stress needs to be laid on treating the patient's general condition as well as his joints.

Although many cases of arthritis will respond to the therapeutic program which has been outlined, not all will do so. We cannot reverse the process and expect to regain a normal joint in any case in which definite damage has been done. In such instances the patient has to learn to live within his limitations, although those limitations may be lessened by the orthopedic surgeon. We do believe that this multi-angled and varied approach to the treatment of joint diseases gives us fewer failures than we have had in the past.

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result after the course of progesterone is stopped. If the amenorrhea is of the continuous-hormonal type in which estrin is continuously present (amenorrheic phase of metropathia haemorrhagica) bleeding will begin 2 to 3 days after the course of progesterone has been stopped.<sup>29</sup> In the normal female, a course of progesterone likewise will be followed in 2 to 3 days by bleeding if the course is terminated before ovulation has occurred, however, if the course ends after ovulation has occurred, the endometrium is maintained by endogenous progesterone produced by corpus luteum of the patient, and the bleeding will not occur until the corpus luteum ceases to function. This may be as long as 14 days after the last dose of progesterone. Progesterone administration, therefore, in these circumstances becomes a test of ovulation. When the bleeding fails to occur within 2 to 3 days after the last injection, but does occur within 14 days after this last injection, ovulation can be assumed to have occurred about 14 days before the start of the bleeding. This response to a course of progesterone is called the *escape phenomenon*. If estrin is known to be present and the patient fails to bleed for more than 14 days after the last dose of progesterone, a presumptive diagnosis of pregnancy can be made.

4 *Parathyroid Extract*—Certain rare cases of hypoparathyroidism are due to resistance to parathyroid hormone rather than to lack of it.<sup>30</sup> These cases can be detected by the failure of the parathyroid hormone to induce phosphorus diuresis. Urine is collected hourly for 3 hours before and for 3 hours after the intravenous administration of 200 units of parathyroid extract and analyzed for phosphorus. In the usual type of hypoparathyroidism the phosphorus in the urine is increased about 10 times by the hormone, in the resistant type less than 2 times the control level.

#### HORMONE IMBALANCE IN MAJOR DISORDERS

A detailed description of the syndromes of endocrine disorder is beyond the scope of this paper. In the following list, the most important abnormalities in the hormone pattern of the more common disorders are given (as far as present concepts allow) in a rather dogmatic fashion.

- 1 *Hypothalamic Precocity*<sup>31</sup> Increased production of luteinizing hormone from the irritation of a lesion in the hypothalamus.
- 2 *Fröhlich's Syndrome* Decreased production of luteinizing hormone from the destruction of a lesion in the hypothalamus, damage to the hypothalamic appetite-controlling center with resulting obesity.
- 3 *Acromegaly* Increased production of the acidophil cell (A) hormones of the anterior pituitary, particularly the growth and the lactogenic hormones.
- 4 *Panhypopituitarism* (Simmonds' Cachexia, Sheehan's Syndrome, Pituitary Dwarfism)<sup>13</sup> Decreased production of *all* anterior pituitary hormones.

# SURGICAL INDICATIONS AND TREATMENT OF PRIMARY CANCER OF LUNG, BRONCHIECTASIS AND LUNG ABSCESS

JOHN W. STRIEDER, M.D.\*

## PRIMARY CARCINOMA OF THE LUNG

THE increasing frequency with which cancer of the lung has been reported as a cause of death in recent years has aroused considerable speculation whether the increase represents a real change in the incidence of this form of malignant neoplasm or is merely the result of improved methods of diagnosis in combination with a more careful search for a disease that has attracted attention because it is reported more frequently than it has been in the past. Dorn states that between 1914 and 1930 the death rate from cancer of the lungs and pleura increased by nearly 400 per cent, as compared with an increase of 20 per cent for all forms of cancer combined. Slightly more than 8000 new cases of primary cancer of the lung are diagnosed and receive treatment for the first time each year. Recently it has been shown that the lung ranks second only to the stomach as the primary site of cancer.

Any male patient of middle age or beyond, who develops cough and expectoration, with or without hemoptysis or blood-streaking, and who cannot be shown to have tubercle bacilli in the sputum, should be considered to have bronchogenic carcinoma until it is proved unequivocally that there is some other reason for his symptoms.

**Diagnostic Procedures.—Roentgenography.**—The first step leading to diagnosis is a roentgenogram of the chest. In most cases, this simple procedure suggests the diagnosis either by indirect evidence, such as atelectasis of a lobe or lobes due to an obstructive bronchial lesion, or by the more positive evidence of an infiltrative hilar lesion or parenchymal tumor. Alexander states that despite the prevailing impression, most circumscribed intrathoracic neoplasms are intrapulmonary and malignant. All pulmonary abscesses and suppurative lesions should be considered as resulting from bronchogenic carcinoma. In general, one may say that the roentgenogram shows the tumor, which may be relatively tiny, less frequently than its result, which usually predominates in the clinical picture. In rare instances, the roentgenogram is negative.

**Bronchoscopy.**—The second step by which a positive diagnosis can best be made before operation is almost always bronchoscopy. Various

\* Assistant Professor of Thoracic Surgery, Boston University School of Medicine, Boston, Massachusetts; Visiting Surgeon in Charge of Thoracic Surgery, Massachusetts Memorial and Boston City Hospitals.

## OBJECTIVES OF HORMONE THERAPY

From these considerations it becomes apparent that hormone therapy must be given with one or more of five objectives in mind (1) The simple replacement of hormone deficiency (2) The stimulation of an underfunctioning gland so that it produces more of its own hormone (3) The inhibition of an overfunctioning gland so that it produces less of its own hormone (4) The neutralization in the end-organ tissues of the effect of a "tissue affecting" hormone (5) The utilization of some specific pharmacologic property of a hormone

HORMONE PREPARATIONS<sup>18</sup>

## GONADOTROPINS

**Chorionic Gonadotropin\* (A P L)**—This naturally occurring substance is a glycoprotein derived from the urine or placenta of pregnant women by modifications of a patented process. It is standardized according to the League of Nations standard 0.1 mg (100 gamma) of the international standard equals 1 international unit. Biologic units of different firms vary considerably in potency depending upon the method of assay employed. Preparations in aqueous solution lose potency on standing for several months at room temperature. The hormone is active by hypodermic administration, but probably not active by oral administration.

**Uses**—Chorionic gonadotropin should be tried as replacement therapy in those conditions in which the luteinizing hormone is decreased, and should be employed as stimulation therapy in those conditions in which the Leydig cells are underfunctioning, ovulation does not occur, or the corpus luteum function is inadequate. Those conditions include functional (but not mechanical) cryptorchidism, Frohlich's syndrome, panhypopituitarism, pituitary amenorrhea, metrorrhagia haemorrhagica, "hypothalamic" amenorrhea of anorexia nervosa and other "nervous" states, hypoleydigism, male climacterium, and recurrent abortion during the first 2 to 3 weeks of pregnancy. In cryptorchidism, the hormone should not be used unless one is prepared to proceed with surgery if an adequate trial (1,000 international units weekly for 6 weeks in frequent small doses) is not followed by descent of the testes, in order to avoid damage that the high abdominal temperature can do to testes that have become partially developed by the therapy (and hence rendered more susceptible to heat).

**Dosage**—Injections of 100 to 750 international units 2 to 3 times weekly are usually sufficient to produce effects in most conditions.

**Pregnant Mare Serum**—The gonadotropins of the pregnant mare are found in the blood serum but not in the urine, and extract of the serum is prepared by a patented process. This substance is an impure

\* Other synonyms: anterior-pituitary-like (A.P.L.) hormone, pregnancy urine (P.U.) gonadotropin, prolan B.

we have had two deaths, a mortality of 9 per cent. Such mortality figures are reasonable ones, and should bring home the fact to the medical profession that the operation of total pneumonectomy for primary cancer does not carry with it an enormous operative risk as has been generally believed. It should be remembered that without operation the risk is 100 per cent.

The question of the age of the patient frequently enters into a consideration of operability. At the present time, there would appear to be no empirical age limit. The general condition, and particularly that of the cardiovascular apparatus is more important than the chronological age.

*Inoperability.*—From an analysis of current statistics and my own experience, only 10 to 25 per cent of cases of bronchogenic carcinoma are operable when first considered for surgery, a sad reflection on the ability of physicians to recognize this relatively frequent disease in its early and favorable states.

The reasons for inoperability, which, as a corollary, mean a late diagnosis and advanced disease, are based on certain findings. These findings have been summarized by Graham as follows:

1. *The presence of bloody fluid.* This usually means invasion of the visceral and parietal pleura by the growth. In most cases, the presence of clear effusions also means inoperability, and the finding of tumor cells in such effusions makes it certain.
2. *Paralysis of the corresponding half of the diaphragm, as determined by fluoroscopic examination.* This usually is due to invasion of the phrenic nerve.
3. *Paralysis of the left vocal cord in cases of left-sided bronchogenic carcinoma.* This usually denotes invasion of the left recurrent nerve as it passes under the arch of the aorta.
4. *Severe pain in the thoracic wall or down the arm.* This is a bad sign and generally is evidence of involvement of intercostal nerves or of the brachial plexus. The presence of a moderate amount of pain, however, should not preclude an exploratory operation.
5. *Bronchogenic evidence of extension of the tumor into the trachea.* This usually contraindicates pneumonectomy, although occasionally it is possible to remove even a part of the wall of the trachea.
6. *The presence of distant metastases.* In exceptional cases, it may prove justifiable to remove both the lung and a solitary metastasis.

#### BRONCHIECTASIS

In a recent paper, Riggins concludes, "The morbidity and mortality of untreated and medically treated bronchiectasis . . . is such that the physician who routinely advises young adults with operable bronchiectasis against surgery is assuming a grave responsibility and in all probability renders his patient a great disservice."

That bronchiectasis is a surgical disease and that most patients in

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of the early disappointing results in the surgery of bronchiectasis are directly attributable to undertaking surgery on the basis of poor or inadequate bronchograms.

The procedure is painless, although, at times, arduous for both the patient and the operator, but it must be persevered in to achieve the desired result. It does not require hospitalization. Not infrequently two or more sittings are necessary before complete and satisfactory bronchograms are obtained.

**Treatment.—Surgical.**—Operation should not be undertaken on febrile patients who are in the acute or subacute phases of a pneumonitis which frequently complicates bronchiectasis and often is the incident which first leads to the diagnosis. Nor should afebrile patients, who have copious foul sputum, be considered for immediate operation. Bitter experience in the early days of this type of surgery has demonstrated that disaster follows such misguided efforts because of the complications of infection of pleura, mediastinum or chest wall due to the presence of virulent anaerobic organisms in this phase of the disease. These patients should be prepared for surgery, as will be discussed below under nonsurgical treatment.

Assuming the patient to be under 35 to 45 years of age, and otherwise presenting no serious contraindications in so far as his general condition is concerned, the indications for and types of operation may be considered under the following headings.

1. *Unilobar disease:* Bronchiectasis localized to one lobe or a segment of a lobe is the ideal indication for surgery. In this situation, lobectomy or partial lobectomy (segmental pneumonectomy) may be recommended with the expectation that the operative mortality will be less than 3 per cent, and the chances for complete cure close to 100 per cent. As has been suggested by the foregoing, disease localized to a definite anatomical segment of a lobe, as the lingula of the left upper or the dorsal or basal divisions of the lower lobes, may be treated by partial lobectomy, thus conserving normal pulmonary tissue.

2. *Multilobar disease:* (a) *Unilateral.* If bronchiectasis is found in more than one lobe of the same lung in such combinations as the right middle and lower lobes, or the left lower and lingula of the left upper, double lobectomy or lobectomy and lingulectomy may be undertaken with little more risk than for single lobectomy. If all lobes of a lung are involved, total pneumonectomy may be offered. Here again, the risk of operation is perfectly respectable—certainly no more than 10 per cent and probably less than 5 per cent.

(b) *Bilateral.* Bilateral lobectomy, in stages, is frequently performed for bronchiectasis. It is now considered routinely in planning the surgical program of suitable bilateral cases. Such combinations as both lower lobes, right middle and left lower lobes, right lower lobe and lingula of left upper lobe, or right lower and middle and left lower lobes have been repeatedly successfully treated by lobectomy in staged



than the conjugated substances, and hence have a shorter action, all free steroids are insoluble in water

USES—Estrogens should be tried as replacement therapy in those conditions in which endogenous estrogenic hormone production is decreased, and as inhibition therapy in those conditions in which the follicle-stimulating hormone is increased. These conditions include the menopause, ovarian-short-stature syndrome, pituitary amenorrhea, panhypopituitarism, acromegaly (to inhibit some of the acidophilic “tropic” hormones), mucous membranes that are atrophic (senile vulvitis, kraurosis vulvae, and atrophic rhinitis) or infantile (juvenile gonorrheal vaginitis), and conditions such as essential dysmenorrhea in which temporary relief may be afforded by inhibition of ovulation. Estrogens in large doses can be used to suppress lactation by inhibiting the anterior pituitary lactogenic hormone, they are reported to be of value in huge doses in controlling toxemias of pregnancy in patients with diabetes mellitus. Estrogens can be used also to neutralize in the peripheral tissues the effects of androgens, dramatic effects can be obtained at times in carcinoma of the prostate by the continuous administration of large doses of estrogen, which by neutralizing the effect of androgens on the neoplasm bring about its regression. *Estrogens should not be given to patients with other types of neoplasm*

It must be remembered that estrogens induce proliferation of the endometrium, therefore, in all females who are given estrogens (except those in whom the uterus has been removed or rendered incapable of bleeding by x-radiation or radium) provision must be made to eliminate the endometrial hyperplasia thus induced. This can be done either by discontinuing the estrogen therapy temporarily, in which case after a suitable interval “estrogen withdrawal bleeding” will occur, or by administering a suitable course of progestogen (v infra) which will convert the proliferative endometrium to the secretory phase and be followed by shedding of the endometrium within 2 to 3 days after the course of progestogen is terminated (for discussion and exceptions see above, Therapeutic Test with Progesterone)

**Crystalline Alpha Estradiol (Dihydroxyestrin)**—This substance is synthesized from naturally occurring estrone, which has been crystallized from the urine of stallions or pregnant mares. No international standard for free alpha estradiol has been established. In terms of biologic potency, estradiol is the most potent estrogen, being two to twelve times as potent as an equal *weight* of estrone depending upon the particular assay technic employed. Free estradiol is more readily absorbed than its conjugated compounds, hence it is best suited for oral and topical administration. It is active by hypodermic injection. Only about one-fifth to one-tenth of the potency by weight is retained, however, when the preparation is given orally. Since it is the most potent estrogen, it has, nevertheless, greater effectiveness weight for weight than other estrogens even by mouth. By hypodermic injection

form of therapy has been limited, but while we have observed temporary improvement in a few cases, there has always been recurrence. Riggins has pointed out the hazard of fibrosis and chronic indurative pneumonitis inherent in this method of treatment. We believe it has little to recommend it, and much to condemn it.

### LUNG ABSCESS

Lung abscess is a common disease but until the middle 1930's it was largely considered to be a medical problem, and the mortality ranged as high as 60 per cent, as reported by various clinics. While it is true that infected emboli lodging in the pulmonary circulation may result in abscess formation, it is now generally accepted that the typical putrid lung abscess is the result of the *aspiration* of the *proper* sorts of infected material. Thus, while the introduction of the ordinary pyogens into the bronchus of a dog will have no effect, the introduction of the scrapings from pyorrhea pockets from the human mouth containing a mixed flora of anaerobes, will result in the formation of putrid lung abscess with a high degree of frequency. Although perhaps 20 per cent of lung abscesses will result in spontaneous cures, the disease is now generally regarded to be primarily of surgical potential and should be so regarded from its inception.

**Diagnostic Procedures.—Sputum Examination.**—As in every instance of pulmonary disease in which there is sputum, this important secretion should be subjected to repeated examinations of concentrated pooled specimens for tubercle bacilli. Foul sputum may occur in rare cases of chronic cavernous pulmonary tuberculosis. On the other hand, occasional acid fast organisms may be present in the purulent secretions of a lung abscess, but it has been pointed out that this may represent sequestration of old healed foci of tuberculosis that chance to be in the field of pulmonary suppuration. Consequently, the findings of a few acid-fast bacilli once or twice in a series of examinations, while adding to the complexity of the problem, does not necessarily mean that the situation which must be met is not that of true lung abscess. It does mean, however, that the physician must be doubly alert in evaluating the evidence. A wide variety of other organisms, including most of the common mouth flora, is invariably present in the sputum. The anaerobic streptococcus is a constant finding and spirochetes and fusiform bacilli can usually be demonstrated in freshly collected specimens. Elastic fibers may be present indicating tissue destruction, but they are also present in the sputum arising from ulcerative lesions of the larynx and trachea.

**Roentgenography.**—One of the most important diagnostic aids in lung abscess is the roentgenogram. By this means, the demonstration of a cavity with a fluid level in the apex of the lower lobe is of prime significance. For purposes of localization, therefore, exposures should

*Dosage*—This varies greatly depending upon the condition to be treated and the sensitivity of the patient. Adequate initial dosage for a moderately severe menopausal state is about 1.66 mg by injection two or three times a week. The dosage can usually be reduced for maintenance therapy. Implantation of 150 to 200 mg in the form of 15-mg pellets will provide adequate estrogenic absorption for 1 to 2 years. In general, larger doses are required for inhibition of a hormone or neutralization of its effect, than for replacement or stimulation therapy.

*Crystalline Alpha Estradiol Dipropionate*—This compound is produced by esterification of alpha estradiol. It is effective over a longer period of time than the benzoate, but is less active on a weight basis. One milligram of estradiol dipropionate is equal to about 3000 Allen-Doisy rat units. No standard unit has been established. It is available for hypodermic injection dissolved in sesame oil.

*Dosage*—In general, 5 mg by injection weekly induces the same effect as 1.66 mg of estradiol benzoate three times a week in a moderately severe menopausal state. Ovulation frequently can be prevented by giving 5 mg on the sixth and again on the sixteenth day after the start of the last menstrual period.

*Crystalline Estrone (Ketoxyestrin, Theelin)*—This naturally occurring estrogen is crystallized from the urine of stallions or pregnant mares. It is standardized so that 1 international unit equals the specific estrus-producing activity of 0.0001 mg (0.1 gamma) of a standard preparation of estrone. On a weight basis it is one-half to one-twelfth as potent by injection as estradiol. Depending on the method of assay employed, 1 mg of estrone has about a potency of 1000 Allen-Doisy rat units.

*Dosage*—Since this estrogen is less potent than the estradiol preparations, larger amounts by weight must be employed to produce the same effects. For initial dosage in a moderately severe menopausal state about 5 to 10 mg by injection two or three times a week should be adequate. Much smaller doses can be used to maintain local effects or to induce manifestations by topical application. As little as 0.02 to 0.4 mg per day by injection may be sufficient to control menopausal symptoms in mild cases. Although by weight the cost of the crystalline estrone preparations is less than that of the crystalline estradiol compounds, the larger amounts required to produce the same effect offset this advantage so that in the end the total cost is about the same.

*Noncrystalline Estrogenic Substances*—These preparations are mixtures of estrogenic substances, but contain essentially estrone; one preparation contains estrone sulfate. They are prepared from pregnant mare urine or from human placenta. By injection they have about the same potency as crystalline estrone, but orally they are only one-twenty-fifth as potent so that 10,000 international units by mouth has about the same clinical effect as 400 international units by injection.

oil will rarely, if ever, enter the abscess cavity. Certain chronic abscesses, with a patent communicating bronchus, may fill well. The value of the procedure, except in isolated instances, is dubious.

*Aspiration.*—Attempts at needling the abscess cavity in acute putrid abscess are fraught with hazard, and mentioned only to be condemned. In such circumstances, aspiration can serve no useful purpose, and the danger of causing a putrid empyema is so great that the procedure should never be undertaken.

*Treatment.*—To Neuhof should go the credit of crystallizing the modern concept of lung abscess as being primarily a surgical disease, and of demonstrating that it may be safely treated in one stage with a mortality of about 2 per cent. With the diagnosis established, then, and definitive surgical treatment the aim, the policy followed in my clinics is to bring the patient to a successful operation at the earliest moment when it is demonstrated that the case under consideration is one that will not heal spontaneously. Procrastination is useless and hazardous in the great majority of cases.

With this in mind, all other forms of therapy should be considered tentative adjuncts until such a decision is arrived at.

*Rest in Bed.*—Obviously all patients with acute lung abscess should be confined strictly to bed.

*Postural Drainage.*—Patients who are raising sputum in any amount should take postural drainage unless the general condition is so poor as to contraindicate it. In order to be effectual, postural drainage is preferably undertaken in such a way as to be as continuous as possible. Thus, if the disease is in the lower lobes, the patient should lie continuously in the prone position with 12-inch blocks under the foot of the bed. Various devices have been evolved to facilitate continuous and intermittent postural drainage. Singer has invented a bed which may be adjusted to any position. For practical purposes, intermittent postural drainage is carried out at two-hour intervals during the day, and the patient is wakened once during the night. The patient must be carefully instructed in order that effectual dependent drainage is obtained. Putting the head over the side of the bed and coughing does not suffice. Frequently, the patient will discover a position which produces the best drainage in his particular case.

*Continuous Oxygen.*—Since anaerobes play an important part in the symbiotic infection in lung abscess, it has been recommended that high concentrations of oxygen be administered continuously by means of a suitable well-fitted mask. Evaluation of this form of therapy is necessarily difficult, but the rationale seems reasonable. We have used it in only one case in which there was temporary improvement but eventual drainage. It deserves further trial.

*Drugs.*—In the past, a wide variety of drugs has been employed in the treatment of lung abscess. The arsenicals, as used in the treatment of syphilis, have been extensively used while the sputum contained

*Dosage*—Doses of 0.5 to 1 mg by mouth or injection daily are effective in controlling the symptoms of a moderately severe menopausal state. Usually 0.1 to 0.5 mg per day are adequate for mild conditions. As much as 10 mg a day has been used for carcinoma of the prostate, 15 mg once or twice daily for several days to suppress lactation, and up to 120 mg daily to control toxemias of pregnancy complicating diabetes mellitus.

#### PROGESTOGENS (PROGESTINS, LUTEINIZING SUBSTANCES)

The term progestogen or progestin refers to a group of compounds with a common action\* of producing progestational changes in the female generative tract. The naturally occurring substance is progesterone, which has been synthesized. An artificial progestogen is preneninolone. The corpus luteum and the placenta produce progesterone, this is converted in the uterus to pregnandiol, which in turn is conjugated in the liver as pregnandiol glucuronide, and then excreted by the kidney as sodium pregnandiol glucuronide. The free substance is not excreted in the urine, it is insoluble in water. Progesterone is supposed to protect the estrogens from destruction. Progesterone is active by injection but completely inactive by mouth. Pregnandiol is also completely inactive by any route of administration. Progesterone is present during the last two weeks of the normal menstrual cycle, and after the first six weeks of pregnancy.

*Uses*—Progestogens should be tried as replacement therapy in those conditions in which endogenous progesterone hormone production is decreased, and as inhibitor therapy in those conditions in which luteinizing hormone production is increased. These conditions include the menopause, ovarian-short-stature syndrome, hypothalamic precocity, states of increased uterine motility (such as habitual [recurrent] or threatened abortion and sometimes dysmenorrhea), and conditions in which ovulation fails to occur such as metropathia haemorrhagica. Progesterone is frequently of considerable value in neutralizing the peripheral effect of estrogens in inducing "premenstrual tension," or hyperplasia of the endometrium such as occurs with metropathia haemorrhagica or continuous exogenous estrogen therapy (v supra). It can be employed as a test for ovulation or for the presence of estrogen (v supra). It is also of value in increasing the development of the breast. In the increased uterine motility states, such as habitual or threatened abortion or dysmenorrhea, progesterone may produce its beneficial effects by inhibiting the action of the posterior pituitary hormone.

*Crystalline Progesterone*—This naturally-occurring substance cannot be economically crystallized from ovarian extracts, therefore, it is synthesized from stigmasterol isolated from soybean oil. It is standardized so that 1 international unit has the specific progestational activity

\* Selye has coined the term "luteoid" to describe this action.

in the hands of an experienced thoracic surgeon is not technically difficult. Following early drainage, improvement is prompt and dramatic in the vast majority of cases. Packing of the abscess cavity until healing occurs is necessary, usually a matter of a few weeks.

3. *Lobectomy and pneumonectomy*.—In long-standing chronic abscess with extensive pulmonary destruction and associated secondary bronchiectasis total extirpation of the diseased lobe, lobes or lung offers the only hope of cure. While the mortality is somewhat higher in this disease than for resections of the lobes or lung in bronchiectasis, for example, it is steadily being lowered and with the use of penicillin promises to be a thoroughly feasible undertaking with a mortality of perhaps under 10 per cent.

*Complications*.—*Empyema*.—Perforation of the abscess which is almost invariably peripherally located, extension of infection to the pleura, or ill-advised attempts at aspiration result in putrid empyema, a common complication. Promptly recognized and immediately treated by extensive rib resection and open drainage, a high recovery rate (85 per cent) may be expected. Temporizing measures such as aspiration or closed drainage result in a much higher mortality (50 per cent).

*Hemorrhage*.—Bleeding of varying degrees frequently occurs as a complication of lung abscess due to the erosion or tearing of a vessel. It is frequently fatal. As a desperate measure, emergency lobectomy may be attempted. If the abscess has already been drained, ligation or cauterization of the vessel or packing of the cavity usually will control the bleeding.

*Spread of the Infection*.—Intrapulmonary bronchogenic spread to the same or to the uninvolved lobes due to spilling of infected secretions is a complication resulting frequently in a fatal fulminating pneumonitis or gangrene. Penicillin has proved of value in this complication. The complication will occur less frequently with early drainage.

*Cerebral Abscess*.—Metastatic spread of the infection to the brain by way of the vertebral veins is a not uncommon complication. In our experience it has been invariably fatal. Recently it has been recognized that ligation of the intercostal veins at the time of drainage of an abscess is a necessary addition to the technic. By this maneuver, the prevention of the spread of septic thrombi into the vertebral veins is accomplished.

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The Leydig (interstitial) cells of the testis produce testosterone which is metabolized in the body (probably in the liver) to approximately equal amounts of androsterone and its isomer etiocholanone, these are then conjugated in the liver as sulfates and probably as glucuronides and excreted as sodium salts by the kidney. Androsterone is biologically active, etiocholanone is not. Dehydroisoandrosterone and androsterone also arise as urinary metabolites of androgens produced by the adrenal cortex of both the male and the female. Dehydroisoandrosterone is also biologically active. Testosterone is usually not excreted in the urine. The testicular and adrenal androgens and their urinary metabolites all contain the steroid nucleus (v supra). In eunuchoid individuals exogenous testosterone also causes an increase in the estrogen excretion in the urine. Testosterone is the most potent androgen known, it is ten times as potent as androsterone and twenty-five times as potent as dehydroisoandrosterone when assayed on the capon comb. The potency of testosterone is nearly equalled, however, by methyl testosterone by the same method of assay. Free testosterone is more rapidly absorbed than its esterified compounds, and hence has a shorter action, free steroids are insoluble in water.

**USES**—Testosterone preparations should be employed as replacement therapy in those conditions in which endogenous androgenic hormone production is decreased. Such conditions include hypogonadism from any cause (eunuchoidism, castration, panhypopituitarism, Frohlich's syndrome, male climacterium and gynecomastia-with-small-testes syndrome), impotency when due to endogenous androgen deficiency, adrenal insufficiency (Addison's disease) and panhypopituitarism in both sexes. Testosterone will induce protein tissue formation in both sexes in all types of disorders, it is the substance par excellence for this.<sup>80</sup> Conditions in which the property can be employed to great advantage include Cushing's syndrome, osteoporosis from any cause (including postmenopausal and senile osteoporosis), where it induces bone matrix formation, delayed growth (although it tends to increase the rate of epiphyseal closure), thyrotoxicosis,<sup>40</sup> in which it will overcome the excess nitrogen loss and reduce the creatinuria, and any state of chronic malnutrition and debility.

Large doses of testosterone can be used to suppress lactation by inhibiting the lactogenic hormone. Testosterone is also useful in female generative tract disorders to neutralize the effect of estrogens on these tissues and to inhibit the follicle-stimulating hormone. These conditions include metropathia haemorrhagica, dysmenorrhea, premenstrual tension, painful breasts and postpartum after-pains. Testosterone preparations should be given cautiously in women to avoid masculinization (v infra). Testosterone will induce development of the tubules but inhibit spermatogenesis while it is being given, after it is stopped spermatogenesis is sometimes increased. Testosterone has not been demonstrated to have any effect on cryptorchidism per se,

## VITAMINS IN PRESENT DAY TREATMENT

HAROLD JEGHERS, M.D., F.A.C.P.\*

THERE appears to be a growing tendency to regard vitamin deficiency as synonymous with nutritional deficiency. This often leads to the erroneous concept that the treatment of any nutritional deficiency consists of the exhibition of one of the many multivitamin capsules or pills now so readily available. Such an approach overlooks the correction of the basic dietary habits responsible for the deficiency and further does not distinguish between the use of natural and complete vitamin substances in contradistinction to the use of a limited number of crystallized or concentrated pure vitamins. It is well to recall at this point that the vitamins now commonly used therapeutically constitute only part of the total vitamins known or still to be isolated and further that vitamins constitute only about a third of the forty or more nutrients required by the human body.

Nutrition is a relatively new and rapidly growing medical science. There is every reason to believe that the practical application of nutritional knowledge will play an ever-increasing role in the medical practice of the future. Its potentialities for preventive medicine appear enormous. There have been many pleas that the physician assume leadership in this field. The praiseworthy results of the application of nutritional principles in the practice of pediatrics are well known. There is much to be said for the continuation of these principles in the practice of adult medicine.

Proper nutrition has been accorded a place, along with heredity, in the control of longevity. The literature contains cautious suggestions that long-continued inadequacy of diet may be a factor in the early development of degenerative diseases. To be truly effective, proper dietary principles must be applied early and continued throughout life. It has been aptly stated that the practice of geriatrics commences where the practice of pediatrics leaves off. Any ill effects of a lifetime of incorrect diet cannot be righted, once old age is reached. The family doctor should make every effort to promulgate this thesis. It is earnestly suggested that an inquiry into a person's habits of eating and recommended dietary changes should be made a routine part of the annual health checkup now being widely recommended to the public.<sup>1</sup>

The widening concept of deficiency disease to include deficiency of

From the Fifth and Sixth (Boston University) Medical Services; Boston City Hospital and the Department of Medicine, Boston University School of Medicine, Boston.

\* Associate Professor of Medicine, Boston University School of Medicine; Physician-in-Chief, Fifth Medical Service, Boston City Hospital; Assistant Physician, Clinical Staff, Evans Memorial, Massachusetts Memorial Hospitals.



compound has the unique property of producing androgenic effects when given by mouth. In the main, it produces the same effects as testosterone, but there are certain differences: (1) it causes more rise in the basal metabolic rate than does testosterone propionate, (2) it causes intense creatinuria due to oversynthesis of creatine, whereas testosterone propionate decreases creatinuria when present, and (3) it is not excreted as a 17-ketosteroid (v supra, Special Endocrine Diagnostic Procedures), whereas testosterone propionate is thus excreted. It is standardized against testosterone propionate, 1 mg of testosterone propionate by injection is about equal to 4 to 6 mg of methyl testosterone by mouth. It is also effectively absorbed through the skin.

**Dosage**—Doses of 40 to 60 mg by mouth daily of methyl testosterone are about equivalent in clinical effect on the eunuchoid patient to 25 mg of testosterone propionate by injection three times a week. However, 10 to 20 mg daily of methyl testosterone orally is adequate dosage for many conditions. Because of its effect on the basal metabolic rate, *methyl testosterone should not be used in thyrotoxicosis*. Topical application of 2 to 4 mg of methyl testosterone ointment once or twice daily is adequate to induce local effects such as growth of axillary hair.

## ADRENAL HORMONES

### CORTICAL HORMONES

Although at least six steroid compounds with cortin-like activity have been isolated as crystalline substances from adrenal cortical extracts, more will probably be found since the residue still contains over half of the original activity. Only one of these crystalline compounds, *desoxycorticosterone*, is available commercially. As has been described (v supra), the adrenal cortex has complex functions dealing with the metabolism and regulation of salts, water, carbohydrate, fat, protein, renal function, and the maintenance of life. None of the isolated compounds possesses all of these functions, there are qualitative and quantitative differences. Complete adrenal cortical hormone replacement therapy, therefore, is not possible with desoxycorticosterone, nor with any of the known crystalline materials. To effect complete replacement at present, whole adrenal cortical extract must be employed, at times in conjunction with desoxycorticosterone. The property which this latter compound exhibits to the most marked degree is that of stabilizing the blood electrolyte balance by favoring the retention of sodium, chloride and water, and the excretion of potassium, this has been termed a "corticomimetic" action.\* Estrogens, progestogens and androgens also exhibit this property to some degree. Urinary cortin-like substances which possess the life-maintaining, growth-promoting

\* Selye has coined the term "corticoid" to describe this action.

to vitamin A.<sup>3</sup> Abnormality of vitamin metabolism is being shown with increasing frequency to be the responsible etiologic factor in a wide variety of hitherto unexplained disorders. This has been especially so with regard to certain skin disease. It is thus apparent that vitamin deficiency will be an ever-present problem in medical practice and apparently one destined to become more complex rather than more simple.

**Dental Causes of Vitamin Deficiency.**—A much neglected phase of medicine is the causal relation of inadequate dentition to nutritional deficiency. This appears to be especially true in the elderly age group. Many older persons and occasionally those from younger age groups, have difficulty chewing solid food, especially meat, due to inadequate dentition. Pyorrhea, loose teeth, dental caries, extensive dental extractions, lack of artificial dentures or artificial dentures not used because of discomfort are common dental causes for vitamin deficiency. I have been strongly impressed with this factor in evaluating the cause of deficiency syndromes in patients studied on the medical wards and in the outpatient department of the Boston City Hospital. It is not uncommon to find patients who for months to years have eaten no meat or other solid foods requiring much chewing. Such persons should receive dental advice and an attempt made to correct this difficulty. If for any reason this is not possible, advice should be given with regard to soft or liquid foods that can be readily eaten but that will nevertheless be nutritionally adequate.

Ill-fitting dentures, aside from causing trouble in eating, may result in constant drooling of saliva. Over a period of time this results in angular fissures at the corners of the mouth, varying degrees of labial change and even glossitis. This syndrome is often mistaken for the changes produced by riboflavin deficiency; in fact Ellenberg and Pollock<sup>14</sup> called it "pseudo-ariboflavinosis." Treatment with vitamin B factors is of no avail and only suitable dental treatment will result in improvement. The "pseudo-ariboflavinosis" is by no means a rare condition.

#### DIAGNOSIS OF VITAMIN DEFICIENCY

Recognition of vitamin deficiency depends on (1) a history of an inadequate diet or presence of some disease or physiologic disturbance interfering with full utilization of ingested food, (2) the presence of specific clinical symptoms and physical signs, (3) laboratory tests and (4) characteristic response to indicated vitamin therapy.

**Laboratory Tests.**—On the whole there are but few specific laboratory tests for the recognition of vitamin deficiency. Furthermore, these procedures are complicated and but rarely available even in well equipped hospitals. Youmans and Patton<sup>4</sup> have given a good discussion of them.

Impaired dark adaptation of the eyes as determined by a photom-

ministration in addition of whole adrenal cortical extract and testosterone propionate (to replace the androgen fraction) will improve the general state of the patient, and markedly increase his resistance to stress, which is related particularly to the "sugar" hormones

During *crisis* more heroic therapy is needed, chiefly with whole adrenal cortical extract (v infra), supplemented with 25 to 35 mg of desoxycorticosterone acetate intramuscularly and parenteral saline and dextrose during the most acute phase. Death usually occurs from hypoglycemia. Withdrawal of testosterone propionate medication should aid during this period. Desoxycorticosterone acetate may be of limited value in controlling the electrolyte balance in shock, but the major indication is whole adrenal cortical extract (v infra), which contains the only available "sugar" hormones

**CAUTION** Overdosage of desoxycorticosterone acetate or excessive sodium intake with it may cause so much retention of sodium and chloride in the extracellular tissues that edema, increased blood volume, hypertension, acute cardiac failure and sudden death may occur or so much loss of potassium that muscular paralysis may appear

**Noncrystalline Whole Adrenal Cortical Extract**—These extracts are prepared from animal glands. They are usually standardized in biologic units, 1 cc contains not more than 3 mg of gland extractives equal to 50 dog maintenance units when assayed by the Pfiffner-Swingle and Vars or the Cartland-Kuizenga methods, and is the concentrate of 40 to 50 gm of fresh adrenal cortical gland tissue. These extracts are usually administered intramuscularly or intravenously but are active by mouth in amounts at least three to four times the parenteral dose

**Dosage**—During the *crisis* of adrenal cortical insufficiency, whole adrenal cortical extract is the treatment of choice. The size of the dose is usually limited by the cost, doses of 100 or even 200 cc per day can be given for several days without harm. The usual dosage during the first 24 hours is 25 cc of cortical extract in an infusion of 2 liters of equal parts of 2 times isotonic saline and 5 to 10 per cent dextrose solution given intravenously at a slow rate, and supplemented with 25 cc of cortical extract and 25 to 35 mg of desoxycorticosterone acetate subcutaneously. This therapy is repeated with decreasing doses of both the cortical extract and desoxycorticosterone acetate for several days. On the third or fourth day, 3 to 6 gm of sodium chloride by mouth daily are started. The patient is watched closely for edema formation or hypoglycemia

During the *noncritical stage* of adrenal cortical insufficiency, the patient is maintained in a better state (v supra) if about 10 cc of whole adrenal cortical extract is given subcutaneously each day. Extra sodium chloride, high carbohydrate diet, and testosterone propionate are also of value during this stage. In shock, whole adrenal cortical extract should be used as during the stage of crisis

pellagra, niacin deficiency encephalopathy, sprue, rickets, osteomalacia, ariboflavinosis syndrome, certain types of cirrhosis, and hemorrhagic hypoprothrombinemia. It has been my personal impression, based on observation of clinical material at Boston City Hospital for the past twelve years, that the above syndromes were more frequent five to ten years ago but are still seen with a fair degree of consistency, and that they are by no means limited to persons addicted to alcoholism. Furthermore, although the grosser degrees of vitamin deficiency have become rarer, milder and subclinical, vitamin deficiencies are still very prevalent. Unfortunately the members of this latter group are considerably more difficult to diagnose, and only by attention to clinical minutiae, a careful dietary history and prompt improvement with disappearance of clinical signs and symptoms following vitamin therapy can they be recognized.

Field and his associates<sup>7</sup> have given an excellent account of the features of atypical and mild pellagra. Ruffin<sup>8</sup> has discussed the recognition of early deficiency states. I have been particularly impressed with the appearance of the tongue as a key to the recognition of mild vitamin deficiency.<sup>9</sup> The lingual papillae, especially the filiform papillae, appear to be sensitive to metabolic changes produced by vitamin deficiency, and tend to desquamate producing a tongue which is smooth and red in appearance. At times it is scarlet red and suggestive of niacin deficiency glossitis; or the papillae may be flattened and the tongue magenta in color, findings indicative of riboflavin deficiency. More commonly the tongue is simply smooth due to loss of papillae and beefy red in color, a condition designated as atrophic glossitis. Atrophic glossitis is frequently present in vitamin B complex deficiency, riboflavin deficiency, pellagra, pernicious anemia, Plummer-Vinson syndrome, sprue, pernicious anemia of pregnancy, chronic dysentery, intestinal stricture or fistula, infestation with broad fish tapeworm and achlorhydria. The presence of atrophic glossitis is an indication for therapy with liver extract or yeast. That the atrophic glossitis is often indicative of B complex deficiency is shown by the striking regeneration of papillae and restitution of the normal pinkish-white color of the tongue when proper therapy is instituted.

There are a wide variety of skin changes indicative of mild to severe vitamin deficiency. These have been discussed in detail elsewhere.<sup>3</sup> Likewise, changes in the external membranes of the eye may give a clue to the diagnosis. Mild thiamine deficiency may resemble neurasthenia or chronic nervous exhaustion.<sup>10</sup> With practice a surprising number of these clinical minutiae can be detected. After proper therapy is instituted disappearance of these minor clinical findings should be periodically searched for as this constitutes suggestive evidence of their deficiency origin.

**Dietary History.**—A reliable dietary history is difficult to elicit, and is much neglected phase of history taking. The

When calcium deposition in bone is inadequate, the serum level is usually unchanged, but may become much elevated if bone formation has been excessive and is suddenly stopped, this latter situation occurs through the loss of the stimulus to bone formation of stresses and strains due to immobilization in rapidly growing children,<sup>42</sup> Paget's disease<sup>43</sup> or hyperparathyroidism with generalized bone disease. When calcium deposition in bone is excessive, the serum level falls, this occurs at times in hyperparathyroidism with generalized bone disease when the excessive resorption from bone has been stopped by parathyroidectomy.

When calcium excretion in the urine is inadequate, the serum level rises, this occurs when calcium resorption from bone is excessive and at times when its deposition in bone is inadequate (v supra). When calcium excretion in the urine is excessive, the serum level falls, this occurs in a selective disease of the renal tubules<sup>44</sup> in which fixed base must be excreted to relieve a chloride acidosis, it causes osteomalacia. Calcium-regulating compounds influence both absorption from the gastro-intestinal tract and resorption from bone, but to different degrees, they affect deposition in bone and excretion in the urine only indirectly.

**Parathyroid Hormone** <sup>45</sup>—The parathyroid hormone exerts its primary effect on the kidney and thereby increases the phosphorus excretion in the urine. This lowers the phosphorus level of the serum, which in turn is restored to normal by an increased resorption of phosphorus from bone, with this, more calcium is resorbed from bone (factor 2 above) so that the serum calcium level rises (hypercalcemia) until finally there is hypercalciuria. If sufficient phosphorus is ingested the serum level is maintained without bone resorption (e.g., hyperparathyroidism without bone disease). Parathyroid hormone has practically no effect on the absorption of calcium and phosphorus from the gastro-intestinal tract (factor 1 above), and hence is not antirachitic. Commercial extracts are prepared from animal glands, and are standardized by biologic assay so that 1 cc exerts the specific activity of 80 to 120 units. Each unit is one one-hundredth of the amount required to raise the calcium level of 100 cc of the blood serum of normal dogs 0.001 gm within 16 to 18 hours. Parathyroid extract is active after an initial injection, but becomes less effective following repeated injections (? "antihormone" formation). When the calcium level must be regulated for considerable periods, dihydrotachysterol or calciferol is the preparation of choice. The extract is inactive by mouth.

**Uses**—For immediate effects only, the extract is of value in all conditions in which the endogenous parathyroid hormone production is deficient: hypoparathyroidism (idiopathic or postoperative) with tetany (low calcium, high phosphorus). It is without effect in the tetany (low calcium, low phosphorus) of rickets or osteomalacia or in

Its use in conjunction with a set of tables giving the caloric value, as well as the carbohydrate, fat, protein, vitamin and mineral content of common foods in terms of household measurements (ounces, cups, teaspoons, slices [of bread], one item of food [e.g., one egg, one pat of butter] etc.) will enable the doctor to make a dietary estimate reliable enough for routine clinical use. Tables of food values are widely available and can be readily secured for reference. In 1941, the Committee on Foods and Nutrition of the National Research Council published its recommended daily allowances for the various dietary nutrients (the so-called "yardstick for good nutrition").<sup>11</sup> These recommendations have been accepted and widely publicized by many authorities on nutrition. Probably every physician has a copy of these recommended daily allowances for specific nutrients in his file since it has been reprinted frequently.

The patient's dietary history can be evaluated by comparison with this recommended daily allowance. Proper attention should be paid to factors likely to increase body metabolism, interfere with gastrointestinal absorption, increase vitamin loss, or impair liver function. Under such circumstances vitamin deficiency may result even though a theoretically adequate diet was eaten. Inquiries should be made concerning the amount of alcohol consumed. Alcoholic patients are especially likely to consume an inadequate diet.

Patients often have trouble remembering the details of their diet. With ambulatory patients not critically ill it is very helpful to have them keep a careful food diary (type of food, amount and how prepared) of all food eaten for a week and postpone the evaluation of their diet until the next meeting. They should be expressly cautioned against any change in their eating habits while under this survey. With patients admitted to a hospital, or with those critically ill and in need of immediate therapy such a plan is not feasible and one must depend entirely on the patient's story.

Inquiry should be made as to the amount of money spent per person per week for food and whether meals are eaten at home or in a restaurant. Smith<sup>12</sup> has given some excellent advice for those who eat away from home. The paper by Guy<sup>13</sup> contains much practical advice with regard to diets. Idiosyncrasies of eating often are the cause of vitamin deficiency. There are many erroneous ideas concerning nutrition widely prevalent which need correcting. A typical example encountered recently was the housewife who separated the heavy cream layer from milk each day and discarded the skim milk portion because of the belief that all the nutrients in milk were contained in the cream layer. She was entirely unaware that the skim milk contained protein and minerals.

The dietary history form is arranged so that the first column lists foods rich in protein, the second foods rich in calcium, the third items high in carbohydrate, but poor in vitamins and minerals, the fourth

intake of calcium and phosphorus (i.e., milk) should be high CAUTION The same comments regarding the overdosage apply as to parathyroid hormone (v supra)

Dihydrotachysterol [A.T. 10\*].<sup>45, 46</sup>—This substance exerts the same primary effect as parathyroid hormone on the phosphorus excretion in the urine (factor 2 above), but in addition has to a mild degree the primary effect of calciferol on the calcium absorption from the gastro-intestinal tract (factor 1 above) Its total action, therefore, is between that of parathyroid hormone and calciferol, but it much more closely resembles the former Dihydrotachysterol is a crystalline derivative of an ultraviolet irradiation product of ergosterol It is potent by mouth, and its effects continue for some days after medication is stopped It is available in oil containing 125 mg per cc (prior to June, 1942, the same preparation was labeled 5 mg per cc because of the presence of then unrecognized inert materials)

*Uses*—This substance can be used in place of parathyroid hormone which it surpasses in the following respects (1) it is crystalline, (2) it can be given indefinitely without becoming less effective, and (3) it can be administered by mouth At present it is rather expensive

*Dosage*—For initial effects in acute conditions, 3 to 4 cc by mouth daily for 3 or 4 days are adequate For maintenance dosage, 1 cc three to four times a week is usually adequate The intake should be high in calcium, low in phosphorus (i.e., milk), 30 per cent calcium chloride solution (4 cc three times a day) or an equivalent amount of calcium gluconate can be given to advantage The serum calcium level should be checked frequently, and the patient should learn to follow his urinary calcium excretion with the Sulkowitch solution<sup>47</sup> CAUTION The same comments regarding overdosage apply as to parathyroid hormone (v supra)

#### POSTERIOR PITUITARY HORMONES

The posterior pituitary gland produces substances with three distinct actions (1) uterine stimulation (oxytocic action), (2) peripheral vasoconstriction (pressor action), and (3) water resorption (anti-diuretic action) Two separate substances have been prepared as extracts of animal glands *pitocin*, which exhibits chiefly the first action and *pitressin*, which has both the second and third Although neither has been crystallized, they are recognized to be polypeptides (minimal molecular weight of about 2000) composed of amino acids, particularly cysteine, tyrosine and arginine Whether these polypeptides represent artificial fractions of one protein hormone is unsettled, there is some indication that the two actions of pitressin may be separated by further fractionation Posterior pituitary preparations are assayed biologically, one international unit (U.S.P. or B.P.)

\* A.T. 10 = antitetanisches Präparat Nr 10

Night blindness and xerophthalmia respond readily to moderate doses of vitamin A (10,000 to 20,000 units) continued for several weeks to two months or more. Skin lesions attributed to vitamin A deficiency or dysvitaminosis A for the most part respond slowly to therapy and require large doses orally (50,000 to 200,000 or more U.S.P. units per day) for months and perhaps years. When large doses are required, capsules of 25,000 or 50,000 units should be prescribed. Persons with dysvitaminosis A may require large doses of vitamin A to maintain improvement. Parenteral vitamin A therapy is but rarely indicated (e.g., in sprue, chronic diarrhea, obstructive jaundice, dysvitaminosis, celiac disease and pancreatic disease). Both bile and pancreatic lipase are necessary for its proper absorption.

**B Complex Vitamins.**—The B vitamins include thiamine, riboflavin, niacin or niacinamide, pyridoxine, pantothenic acid, choline, inositol, para-aminobenzoic acid, folic acid, biotin and perhaps others. Although almost all of these are available commercially in synthetic form, only thiamine, riboflavin and niacin have well established uses in clinical practice. There is a growing but still controversial literature concerning the others.

Thiamine, riboflavin and niacin are prescribed by weight. The recommended dosage for therapeutic purposes should be at least several times the optimal daily requirement as recommended by the Committee on Foods and Nutrition of the National Research Council.<sup>11</sup> For example, a 70 kg. man, moderately active, needs 1.8 mg. of thiamine, 2.7 mg. of riboflavin and 18 mg. of niacin daily. For gross deficiency of these vitamins, 10 to 30 mg. of thiamine, 5 to 20 mg. of riboflavin and 100 to 300 mg. of niacin could be prescribed. Ordinarily these vitamins are given orally in daily divided doses. Where indicated they may be given parenterally. Parenteral preparations are commercially available which contain adequate amounts of thiamine, riboflavin, niacin, pyridoxine and calcium panthothenate. Niacinamide is commonly used in place of niacin (nicotinic acid) unless the vasodilator effect of the latter substance is specifically desired. The therapeutic dose of the B vitamin should be continued for one to several weeks or until the clinical deficiency is corrected, after which the amount required daily can be reduced to the optimal daily requirements.

While the synthetic B vitamins are indicated in the treatment of gross deficiency syndromes it is well to supplement the therapeutic regimen with one of the natural sources of the complete B complex. If the ordinary daily diet is to be supplemented, vitamin B complex in natural form is preferable to a capsule containing a limited number of the synthetic B vitamins.

**Natural Sources of B Complex.**—There are a number of natural substances containing all the members of the vitamin B complex. These include liver extract, wheat germ, brewers' yeast, autolyzed yeast and



patients, these include pallor, nausea, belching, cramps, diarrhea, uterine cramps, tinnitus, anxiety, albuminuria, eclamptic attacks, mydriasis, amaurosis and unconsciousness. These preparations are contraindicated in epilepsy, hypertension, coronary artery and other vascular disease, pregnancy, and usually during the first two stages of labor.

### THYROID HORMONE

The thyroid hormone is secreted by the follicle cells of the thyroid gland, stored in the follicles, and released into the circulation as needed, when the follicles are empty and the demand great the hormone may be secreted directly into the circulation. The secretion is regulated humorally by the thyrotropic hormone (v supra). The formation of the hormone is not clearly understood. It is believed that tyrosine combines with iodine to make *diiodotyrosine*, which, in turn, is converted into the amino acid, *thyroxin*, either (a) by condensation together of two diiodotyrosine molecules or (b) by iodination of diiodothyronine (diiodotyrosine combined with phenol). In any event, thyroxin and diiodotyrosine are linked together with other amino acids to form a peptide (considered to be the true hormone), this then combines with other amino acids to form *thyroglobulin* (colloid). When thyroglobulin undergoes natural breakdown, the biologically active peptide is released, when it is broken down by acid hydrolysis or proteolytic enzymes, the active thyroxin and the inactive diiodotyrosine are released. The biological activity of the thyroglobulin molecule is apparently due to its total organic iodine content, of which about 30 per cent is in the form of thyroxin and about 70 per cent in the form of diiodotyrosine. It has been estimated that about 0.33 mg of thyroxin (about 50 mg of thyroglobulin) is elaborated in 24 hours, to produce this the body needs about 0.2 mg of iodine per day.

As has been described (v supra), the natural thyroid hormone has manifold actions, including particularly a calorogenic action, an effect on growth, and a role in the metabolism and regulation of salts, water, carbohydrate, fat, and protein, it is required for normal function by every tissue in the body. How it acts is unknown. Some investigators believe that it acts peripherally as a catalyst on individual cells, some that it acts upon the vegetative centers in the brain stem. Regardless of the route of administration, a single dose of thyroid hormone requires about 24 hours to produce a noticeable effect, about 10 days to induce a maximal response, and about 70 days to complete its action. Therefore, daily medication is cumulative. Thyroid hormone apparently is completely destroyed in the body, probably in the liver, no thyroxin is demonstrable in the excreta (except after the administration of large doses), the excretion of diiodotyrosine has not been settled. The iodine of the thyroid hormone is excreted by the kidney, liver, intestines, skin, lungs, milk and saliva, when very large doses of

Fifteen grams of brewers' yeast powder is added to each quart of mixture. This amount gives no detectable taste, adds approximately 7.2 gm. of protein and 5.8 gm. of carbohydrate, and is generally accepted by patients.

#### FORMULA FOR SKIM MILK MIXTURE

	Carbohydrate	Protein	Fat
	Gm.	Gm.	Gm.
6 oz. orange juice.....	16.95		
4 oz. Karo syrup.....	88.8		
6 egg whites.....	.....	25.8	.6
100 gm. skim milk powder.....	38.8	35.4	1.7
24 oz. skim milk.....	33.9	25.8	5.1
Total.....	178.45	87.0	7.4
Calories.....	1128		

The vitamin content of the skim milk mixture as given in the formula with added yeast powder is approximately 2.5 mg. of thiamine, 1.8 mg. of riboflavin, 6.5 mg. of niacin, 1.5 mg. of pantothenate, 0.6 mg. of pyridoxine, 45 mg. of ascorbic acid as well as other B complex factors. The vitamins except niacin and A and D, about equal the optimum daily allowances recommended by the National Research Council.

The protein is biologically highly active. The fat is low, but the amount of carbohydrate and the total calories are low in proportion to the amount of protein present. This mixture has been widely used for diets of patients with liver disease because of its high protein and carbohydrate and low fat content. It is very useful as a high protein-high vitamin supplement to the patient's routine diet.

#### FORMULA FOR WHOLE MILK MIXTURE

	Carbohydrate	Protein	Fat
	Gm.	Gm.	Gm.
32 oz. whole milk.....	45.2	34.4	32
100 gm. skim milk powder.....	38.8	35.4	
3 whole eggs.....		18.0	18
Total.....	84.0	87.8	50
Calories.....	1137		

This mixture can likewise be supplemented with Karo syrup, orange juice, and brewers' yeast as described for the skim milk mixture and these add to the protein and carbohydrate value. Likewise it may be

ments are 0.17 to 0.23 per cent iodine in a form peculiar to that which exists in the thyroid gland. It may be assayed biologically by employing the rate of carbon dioxide production in mice, the rate of oxygen consumption in rats, the increased sensitivity of rats to oxygen deficiency, the rate of metamorphosis of tadpoles (Gudernatsch), the decreased sensitivity of mice to acetonitrile poisoning, or the response of myxedematous patients<sup>4</sup>. The active component is thyroglobulin, an iodine-containing globulin with a molecular weight of 675,000.

**Dosage**—For complete replacement therapy, 0.1 to 0.2 gm by mouth daily is usually adequate. It is important to know the iodine content of the brand that is administered: preparations conforming to USP standards (e.g., Armour's) have about 0.2 per cent iodine, the preparation marketed by Parke-Davis about 0.3 per cent, and that marketed by Burroughs Wellcome 0.08 per cent (British Pharmacopoeia specifies 0.09 to 0.11 per cent organic iodine and not more inorganic iodine than 10 per cent of the total iodine). **CAUTION** The same comments regarding overdosage apply as to crystalline thyroxine (v supra).

#### PANCREAS HORMONE INSULIN

This naturally occurring protein (molecular weight 35,100) is derived from animal glands (beef, sheep, hogs). It contains the amino acids leucine, glutamic acid, cystine, tyrosine, histidine, arginine, lysine, proline, phenylalanine, and possible methionine. Its activity depends on the integrity of the protein molecule and is destroyed by attempts at fractionation. Crystals have been obtained by the combination of insulin with zinc, cobalt, nickel and cadmium. It is standardized biologically by the induction of hypoglycemia in rabbits\* or by the appearance of convulsions in mice; 1 unit is the effect of 0.125 mg of standard dry insulin hydrochloride or 0.04 mg of crystalline zinc insulin. One unit, on the average, will promote the metabolism of approximately 1.5 gm of dextrose. It is estimated that the pancreas produces about 45 to 80 units daily when an average diet is consumed and about 8 units daily during starvation. The hormone is rapidly destroyed in the body although a small amount may be excreted in the urine. Insulin preparations should not be used longer than 2 years after the date of distribution stamped on the package. The hormone is active by hypodermic administration, but only slightly and variably active by ingestion.

**Uses**—Insulin is specific replacement therapy for diabetes mellitus. Its pharmacologic action of stimulating appetite is employed in malnutrition, its effect in inducing hypoglycemic shock is used in psychiatric disorders. Insulin is employed in the diagnosis of disturbances in carbohydrate metabolism in the "Insulin Tolerance Test" (v supra).

\* One unit is the amount of crystalline zinc insulin required to reduce the normal blood sugar level of 120 to 45 mg per cent in a normal 2-kg rabbit fasted 24 hours.

# THE PRESENT STATUS OF SULFONAMIDE THERAPY

FRANCIS C. LOWELL, M.D.\*

APPROXIMATELY six years have passed since the sulfonamide drugs became available for use on a scale sufficiently large to make clinical evaluation possible in a wide variety of diseases. During this period, new forms of sulfonamides have made their appearance from time to time, all of them, however, resembling each other in their mode of action and most of them differing principally in their solubility, their rate of absorption from the gastrointestinal tract and their rate of excretion by the kidney. All the commonly used sulfonamides are inhibited in their antibacterial action by para-aminobenzoic acid and to a variable extent by pus and necrotic tissue. These drugs also have in common the tendency to cause toxic reactions and careful supervision of the patient receiving a sulfonamide is necessary.

The biggest single change in the use of the sulfonamide drugs has been brought about by the advent of penicillin, which has recently become available for general use in this country. This can only be given by repeated injection at the present time, a fact which restricts its use and makes a sulfonamide the drug of choice under certain circumstances, even when penicillin may be more effective, and even though penicillin has the further advantage of producing very few toxic reactions.

With sulfonamides and penicillin available, the indications for serum treatment of infections due to such organisms as the pneumococcus and meningococcus are indeed rare. It is to be remembered, however, that gram-negative organisms, such as the influenza bacillus and Friedländer's bacillus, are entirely unaffected by penicillin and certain infections caused by them may best be treated with a sulfonamide and a specific antiserum.

The sulfonamides have been used for the prevention of recurrences of rheumatic fever and in the armed forces as a means of stopping or preventing epidemics of meningococcal and streptococcal infections. With proper control of the conditions under which the drugs are given, good results have been obtained with few and usually only mild toxic reactions. However, it seems unlikely that these measures can be effectively applied to civilians under the usual conditions of medical practice.

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From the Evans Memorial, Massachusetts Memorial Hospitals and the Department of Medicine, Boston University School of Medicine.

\* Assistant Professor of Medicine, Boston University School of Medicine; Associate, Evans Memorial and Assistant Visiting Physician, Massachusetts Memorial Hospitals.

commended because it has a slightly longer duration of effect and is less likely to induce "insulin allergy" or "insulin resistance" (v supra, "Antihormones") It has almost completely replaced amorphous insulin

*Dosage*—The same dosage is advised as of the amorphous insulin

**Protamine Zinc Insulin**—This is an aqueous suspension of insulin combined with protamine and minute quantities of zinc It is available in strengths of 40 to 80 units per cc The protamine has the effect of slowing the rate of absorption so that a single dose is effective for 24 to 36 hours or longer For this reason daily dosage is cumulative The active material is a finely divided white precipitate which *must be mixed thoroughly before injection*, it should *never be given intravenously*

*Dosage*—Patients using amorphous or crystalline zinc insulin can be shifted to protamine zinc insulin by administering two thirds of the dose, and supplementing, if necessary, with crystalline zinc insulin The dose can be given at morning or night, several days should elapse between each change in dosage In *diabetic acidosis* (v supra) a single dose (about 50 units) should be given at the start of treatment Protamine zinc insulin should not be used to improve appetite or to induce "insulin-shock" therapy **CAUTION** Overdosage of protamine zinc insulin will lead to the same manifestations as overdosage of amorphous or crystalline zinc insulin, however, because of the longer action of the protamine preparation the reactions also are more prolonged and hence more serious They require continuous treatment with dextrose by vein and by mouth for some hours to be certain that the untoward effects will not recur

#### INERT PREPARATIONS

From what has been said it should be apparent that many free steroids are inert by mouth This is true particularly of progesterone and testosterone Therefore, "corpus luteum pills," "ovarian residue pills" and the like are completely inactive Synthetic preparations must be relied on because remarkably little natural hormone is present in the parent gland at any one time It has been estimated that one ton of testes is needed to produce 90 to 270 mg of testosterone,<sup>48</sup> that tons of ovaries per dose are needed to secure estrogenic effects, and that only 1 part of progesterone is present in 40,000 in the human corpus luteum<sup>49</sup> or 1 part in 750,000 in the placenta<sup>50</sup> Furthermore, all aqueous extracts of hormones for oral use should be viewed with suspicion because the free steroids are largely insoluble in water and the conjugated forms which are soluble *are inactive by mouth* Included in the list of inert substances are preparations of desiccated ovary, testicle, thymus, pineal gland, prostate and mammary gland There is no justification for the use of these substances in view of the potent preparations available Frank<sup>51</sup> has summed up the situation by stating that "such 'things' as desiccated ovary, desiccated testis, thymus and anterior pitui-

Fluids may be given orally in the form of soups, milk, fruit juices, normal saline and water or parenterally as saline, glucose and water in combination, so as to provide 10 to 15 gm. of salt and a sufficient volume of fluid. In the presence of dehydration, the initial dose of sulfonamide should be accompanied by, or even preceded by, a sufficient quantity of fluid to insure hydration of the patient.

**Renal Complications.**—Crystalluria, hematuria, renal colic, oliguria and anuria are complications of sulfonamide therapy, listed here in order of increasing seriousness. As renal complications are more frequent than any others during sulfonamide therapy, they should be watched for carefully. *Crystalluria*, that is, the finding of sulfonamide crystals in the spun sediment of freshly voided urine specimens, indicates that the conditions are present which predispose to renal complications and steps should be taken to increase the urinary output and to render the urine alkaline. The same may be said of *microscopic hematuria*. In neither instance is cessation of sulfonamide therapy necessary. *Gross hematuria, renal colic, oliguria* and *anuria* require immediate cessation of sulfonamide therapy followed as well by those measures just mentioned. In the presence of anuria, ureteral lavage with a warm alkaline solution may be indicated.

There is considerable evidence that the administration of alkali with a sulfonamide will reduce the tendency to those renal complications resulting from precipitation of the sulfonamide in the kidney. The base acts by raising the  $pH$  of the urine to 7 or higher, thereby increasing the solubility of the sulfonamide, especially the acetylated form, in the urine. Sodium bicarbonate may be given by mouth or sodium lactate (100 cc. of one-sixth molar sodium lactate solution is equivalent to 1.4 gm. of sodium bicarbonate) may be added to the solution of sulfonamide for parenteral administration. The amount of sodium bicarbonate necessary to raise the  $pH$  of the urine differs widely among patients and it is convenient and helpful to follow the urinary  $pH$  with nitrazine paper. In adults, an initial dose of 6 gm. and a daily dose of 15 gm. in twenty-four hours is usually sufficient. Patients who are nauseated and who are receiving a sulfonamide by mouth, may object to taking sodium bicarbonate in addition. Under such circumstances it may be wiser for the doctor to omit bicarbonate and to center his attention on insuring an adequate urinary output.

Severe renal damage during sulfonamide therapy may arise on some basis other than mechanical damage and obstruction due to precipitation of crystals. The pathogenesis of this complication is not clear. There develops tubular degeneration with increasing renal failure which may be fatal. The factors predisposing to this are not known but large dosage and high blood levels are not a *sine qua non*. The condition is characterized clinically by a decreasing urinary output, albuminuria, microscopic hematuria and white cells in the sediment.

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treatment may then be modified in the light of the bacteriologic findings. Grouping or typing of organisms should be carried out when possible.

**Pneumonia.**—In view of the difficulty in distinguishing the bacterial pneumonias from primary atypical pneumonia (presumably caused by a virus), it seems advisable to treat all cases of severe or moderately severe pneumonia with chemotherapy at the outset. If after 48 to 72 hours of treatment there is no response and the clinical picture and bacteriologic findings indicate the absence of bacterial infection, chemotherapy may be stopped. The more severely ill patients should be hospitalized. Whether penicillin, sulfonamide, or both should be used will depend on the causative agent. If the cause is in doubt, especially if the patient is very ill, both penicillin and sulfonamide may be given.

It is to be noted that two important causes of pneumonia, the influenza bacillus and Friedländer's bacillus, are entirely unaffected by penicillin. Treatment here consists in full dosage of sulfadiazine or sulfamerazine and possibly the use of specific antiserum. This last is available for Friedländer's bacillus, type A and B, and for influenza bacillus, type B. The identification of types may be facilitated when it is recalled that the capsule of the influenza bacillus, type B, usually swells in the presence of type XXIX pneumococcus typing rabbit serum and often in the presence of type VI typing serum, and that of Friedländer's bacillus, type B, swells in the presence of type II pneumococcus typing rabbit serum. This information may be useful as pneumococcus typing serum is available in most laboratories.

**Meningitis.**—The sulfonamide drugs are extremely effective in *meningococcic meningitis* and there is little reason at present to believe that penicillin alone would give better results. As the organism is highly sensitive to both drugs, combined therapy should be given to severely ill patients, especially those having a rash.

The treatment of meningitis due to the pneumococcus and streptococcus, organisms which are also susceptible to both sulfonamide and penicillin, consists in full dosage of a sulfonamide, preferably sulfadiazine, the intramuscular or intravenous administration of 200,000 units of penicillin daily and the intrathecal injection of 20,000 units of penicillin at twelve-hour intervals. Bacterial meningitis, especially pneumococcic, has a strong tendency to relapse when treatment is stopped, and for this reason treatment should be continued for at least ten days after culture of the spinal fluid has become negative, the sugar has returned to normal, and the cell count has fallen to 100 or less with a predominance of lymphocytes. Early diagnosis and treatment are of the utmost importance.

*Pneumococcic meningitis* still carries a high mortality and early intensive treatment is imperative. In addition to penicillin and sulfonamide therapy as outlined above, specific serum is available for the various pneumococcic types. If it is decided to give serum, this may



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crete the drug in the urine more rapidly than others. The only way to recognize this difficulty is to make repeated determinations of the blood level. The dosage of drug may be increased until satisfactory levels are obtained. Patients receiving a sulfonamide by mouth who fail to attain adequate blood levels may be given supplementary doses of two or more grams intravenously.

The development of *sensitivity* to a sulfonamide drug, usually occurring after five or more days of treatment, may cause the persistence of fever and thus simulate a therapeutic failure. If a rash also appears, the correct cause of the fever is readily suspected, but in the absence of any skin manifestations there are no definite criteria by which one can recognize the condition. If drug fever is present, a fall in temperature follows cessation of therapy. This fall is rapid in patients who have been receiving sulfathiazole, occurring in twelve to twenty-four hours, but the fall is more delayed in the case of sulfadiazine and sulfamerazine where the rate of excretion is slower.

Occasionally the infecting organism is a *sulfonamide-resistant* strain. Larger doses or a different sulfonamide may be tried but usually little is gained in this way. Penicillin should be given if the organism is susceptible to this drug.

Pathogenic organisms are often present in the throat or elsewhere even though they may be playing no part in the patient's infection. This is a common source of *error in diagnosis* and when the correct cause of the infection is found, more effective treatment can often be given.

Patients who have a *complication*, such as empyema, abscess, osteomyelitis or endocarditis, may continue to have fever and leukocytosis in spite of intensive therapy. Renal infections associated with *stone* or *congenital defects* may also respond poorly to therapy. Treatment of the local condition is usually required before complete recovery will take place.

#### SUMMARY

The sulfonamide drugs are best given in full therapeutic doses in the treatment of most acute infections. Repeated determinations of the blood level are necessary in order to insure safe and adequate treatment. Toxic reactions must be recognized early.

The present-day treatment of many infectious states can be extremely effective when the cause and severity of the infection are known and when appropriate treatment is started early.

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## LABORATORY FINDINGS IN THE BLOOD AND URINE IN HEALTH AND DISEASE

STANLEY E. BRADLEY, M.D.\*

As medical knowledge expands, the position of the laboratory in every field of medical practice becomes increasingly important. Its services are indispensable in modern diagnosis and treatment, particularly since chemotherapeutic methods of halting disease processes and of repairing the ravages of disease have proved their worth and come into universal use.

The large number of procedures carried out in the routine laboratories of even small hospitals each year is indicative of this importance, but it is also indicative of misuse. It is apparent everywhere that many physicians use laboratory facilities unthinkingly. Laboratory studies are often demanded routinely on a hit-or-miss basis in the hope of easy diagnosis, frequently with the aim of impressing and pleasing the patient. This is unfortunate because it results in unnecessary labor in the face of manpower shortages, in a deterioration of standards and in unreasonable expense. In the last analysis, diagnosis devolves upon the physician, depending upon his observational skill and his perception of significant facts in data culled from the history, the physical examination, and, finally, the laboratory study. This task can never be safely shifted to the shoulders of laboratory personnel. On the other hand, there is abundant evidence that available facilities are not used efficiently. Not infrequently, intuition plays too large a role in guiding treatment. This is to be deplored because the accurate adjustment of chemotherapy requires an accurate knowledge of the system under treatment.

One important cause of these abuses lies in the staggering number of procedures now available and in the difficulty of keeping in mind the normal figures and causes of deviations. The tables that follow have been compiled with the purpose of providing for ready reference the range of normal values of a large number of blood and urine constituents. A list of some of the more important disorders in which changes are observed has been added. The tables are based on the physiological systems of the body that are disturbed by disease. It can be seen that a view of these data as primarily expressive of physiological states rather than of etiological factors is implicit in this arrangement. It is true that certain tests may be of great value in clari-

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From the Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine, Boston.

\* Instructor in Medicine, Boston University School of Medicine; Assistant Physician, Evans Memorial, Massachusetts Memorial Hospitals.

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pH	arterial.....	7.30-7.49
	venous.....	7.33-7.52
Specific Gravity	.....	1.0254-1.0288
Proteins—	total.....	6.5-7.5 gm. per 100 cc.
	albumin.....	3.8-4.4 gm. per 100 cc.
	globulin.....	2.2-3.4 gm. per 100 cc.
	A/G ratio.....	1.4-2.2
	fibrinogen.....	0.2-0.6 gm. per 100 cc.
Blood Volume—	adults.....	2990-6980 cc. (4635 cc.)
	females.....	46.3-85.4 cc./kg. body weight
	males.....	66.2-99.7 cc./kg. body weight

## IN DISEASE

- Na (+) Vomiting, renal insufficiency, nephrotic syndrome, occasionally cardiac decompensation, Cushing's syndrome, adrenocortical tumor.
- Na (-) Renal insufficiency, vomiting, diarrhea, excess sweating, starvation, diabetes mellitus, pregnancy, nephrotic syndrome, Addison's disease.
- Ca (+) Pyloric obstruction, hyperparathyroidism, acidosis, polycythemia.
- Ca (-) Renal insufficiency, post-parathyroidectomy, infantile tetany, oxalic acid poisoning, osteomalacia, rickets, starvation, diarrhea, late pregnancy, nephrotic syndrome, steatorrhea, hyperthyroidism.
- K (+) Addison's disease, renal insufficiency, shock.
- K (-) Periodic familial paralysis, fever, nephrotic syndrome, Cushing's syndrome, adrenocortical tumor.
- Mg (+) Renal insufficiency.
- Mg (-) Occasionally in epileptic convulsion.
- HCO<sub>3</sub> (+) Alkali ingestion, vomiting, pulmonary emphysema, morphine poisoning, pneumonia, occasionally renal insufficiency.
- HCO<sub>3</sub> (-) Renal insufficiency, diarrhea, vomiting, excess sweating, starvation, dehydration, acid ingestion, oil of wintergreen and methyl alcohol poisoning, decompensation, Addison's disease, anesthesia.
- Cl (+) Diuresis due to chloride and sulfate diuretics, anesthesia, prolonged hyperventilation (hysterical and postencephalitic).
- Cl (-) Addison's disease, starvation, vomiting, water and mercurial diuresis, alkalizing salts, diabetes mellitus, pneumonia, occasionally diarrhea, nephrosis and acute nephritis.
- HPO<sub>4</sub> (+) Renal insufficiency, post-parathyroidectomy, occasionally osteomalacia, rickets and acute yellow atrophy of liver.
- HPO<sub>4</sub> (-) Hyperparathyroidism, rickets, osteomalacia, steatorrhea.
- SO<sub>4</sub> (+) Renal insufficiency, intestinal obstruction.
- Organic Acids (+) Starvation, diabetes mellitus, renal insufficiency, vomiting, diarrhea, shock, anesthesia, cardiac decompensation—See Table 2 for further data.
- Total Proteins and Specific Gravity (+) Shock in dehydration, vomiting, diarrhea, excess sweating, burns, peritoneal injury, etc., myxedema, lymphogranuloma venereum, syphilis, Boeck's sarcoid, miliary tuberculosis, leprosy.
- (-) Nephrotic syndrome, shock due to blood and plasma loss, steatorrhea, chronic intestinal obstruction, hepatic disease, starvation, acute nephritis, cardiac decompensation.
- Albumin follows total protein
- Globulin and Fibrinogen (+) Multiple myeloma, kala azar, carcinomatosis, schistosomiasis, diphtheria immunization, various inflammatory states.
- Plasma Volume (+) Cardiac decompensation, polycythemia, certain types of chronic anemia, pregnancy.
- Plasma Volume (-) Shock, dehydration, renal insufficiency, chronic anemia, vomiting, diarrhea excess sweating.

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- Hypoglycemic response*—Hypothyroidism, hypopituitarism, Addison's disease, steatorrhea, diarrhea.
- Glucose Tolerance Test (intravenous)  
*Hyperglycemic response*—As in oral.  
*Hypoglycemic response*—As in oral except that steatorrhea and diarrhea have no effect on curve.
- Insulin Tolerance Test  
*Insulin resistance*—(delayed or absent fall)—Cushing's syndrome, hyperpituitarism (acromegaly, etc.). Insulin resistance of unknown etiology.  
*Hypoglycemic unresponsiveness*—(delayed or absent terminal rise)—Hyperinsulinism, Addison's disease, hypopituitarism.
- Lipase  
 (+) Pancreatitis, pancreatic neoplasm.
- Diastase  
 (+) Acute pancreatic disorders (trauma, pancreatitis, etc.), mumps.
- Congo Red Test  
 Less than 70 per cent of dye in blood after 30 minutes—amyloidosis, massive proteinuria.
- Phosphatase—acid  
 (+) Carcinoma of prostate.
- Phosphatase—alkaline  
 (+) Neoplasm of bone, Paget's disease of bone, fragilitas ossium, rickets, osteomalacia, hyperparathyroidism, biliary obstruction.
- Creatinine  
 (+) Renal insufficiency (except when acute or upon obstructive basis).
- Creatine  
 (+) Renal insufficiency.
- Creatine Tolerance Test  
 Increased retention—Hypothyroidism, myotonia congenita.  
 Decreased retention—Hyperthyroidism, myotonia atrophica, progressive muscular atrophy.
- "Hormonal" Iodine  
 (+) Hyperthyroidism, hyperpituitarism (acromegaly, etc.).  
 (—) Hypothyroidism, hypopituitarism.
- 17-Ketosteroids  
 (+) Adrenal cortical carcinoma, adrenal cortical hyperplasia, testicular interstitial cell tumor.  
 (—) Hypothyroidism, hypopituitarism, Addison's disease.
- Chorionic Gonadotropin—A-Z Test—positive  
 Pregnancy, hydatid mole, chorionepithelioma.
- Nonprotein Nitrogen and Urea Nitrogen  
 (+) Renal insufficiency, hyperthyroidism, shock, hemorrhage, fever, vomiting, diarrhea, cardiac decompensation, dehydration, pregnancy.
- Urea Nitrogen  
 (—) Starvation, diuresis, acute yellow atrophy.
- Uric Acid  
 (+) Renal insufficiency, gout, toxemia of pregnancy, leukemia.
- Ketone Acids  
 (+) Diabetes mellitus, starvation, alkalosis, vomiting.
- Lactic Acid  
 (+) Extreme exertion, cardiac decompensation, shock, diabetes mellitus.
- Pyruvic Acid  
 (+) Thiamine deficiency, cardiac decompensation, fever, diabetes mellitus, hyperthyroidism.
- Phenols  
 (+) Renal insufficiency, intestinal obstruction, pernicious anemia.
- Ammonia  
 (+) Renal insufficiency.
- Amino Acid Nitrogen  
 (+) Acute yellow atrophy, occasionally renal insufficiency, leukemia.  
 (—) Nephrotic crisis.
- Guanidine  
 (+) Renal insufficiency.
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**Icterus Index**

(Up to 20—subclinical jaundice). Jaundice, carotinemia.

**Bilirubin (quantitative)**

(+) Jaundice—indirect (+) in proportion to direct—hemolytic jaundice; direct (+) in proportion to indirect—obstructive, hepatotoxic jaundice (less marked disproportion).

**Cholesterol**

(+) Hypothyroidism, biliary obstruction, cirrhosis, diabetes mellitus, nephrotic syndrome, renal insufficiency, hypercholesterolemic lipoidoses (xanthomatosis), cardiac disease.

(–) Renal insufficiency, any extensive hepatic disease, hyperthyroidism, fever, cachexia, steatorrhea, anemia.

**Neutral Fat and Fatty Acids**

(+) Hypothyroidism, anemia, diabetes mellitus, nephrotic syndrome.

(–) Hyperthyroidism.

**Lipoid Phosphorus**

(+) Diabetes mellitus, nephrotic syndrome.

(–) Anemia.

\* The multiplicity of liver function tests renders complete tabulation impossible. Only the more reliable and commonly used procedures are listed.

**4. RENAL FUNCTION TESTS****IN HEALTH****Clearance Tests**

Inulin Clearance	} Glomerular Filtration Rate (GFR)	Male....	110–150 cc./min.
Mannitol Clearance		Female...	105–132 cc./min.
Diodrast Clearance		Male....	560–830 cc./min.
P - aminohippurate Clearance	} Renal Plasma Flow (RPF).....		
		Female...	490–700 cc./min.
Filtration Fraction (FF) (equals GFR/RPF).....		Male....	17– 21 per cent
		Female...	17– 23 per cent
Urea Clearance (Cu).....		Standard.	40– 65 cc./min.
		Maximal.	60–100 cc./min.
Maximal Glucose Reabsorptive Capacity (TmG).....		Male....	300–450 mg./min.
		Female...	250–350 mg./min.
Maximal Diodrast Excretory Capacity (TmD).....		Male....	43– 59 mg./min.
		Female...	33– 51 mg./min.
Phenolsulfonphthalein Excretion.....			40–60 per cent in first hour;
			60–85 per cent in second hour.
Dilution-Concentration Test....			1.004–1.025

**IN DISEASE**

GFR	(–)	Glomerulonephritis, nephrosclerosis, and other renal diseases, shock, anemia.
RPF	(+)	Fever, certain cases of acute diffuse glomerulonephritis.
RPF	(–)	Glomerulonephritis, nephrosclerosis, and other renal diseases, shock, anemia, apprehension, pressor drugs.
FF	(+)	Essential hypertension, nephrosclerosis, pressor drugs.
FF	(–)	Glomerulonephritis, fever, orthostasis, shock, anemia.
Cu	(+)	Fever, rising slope of diuresis curve, after protein meal.
Cu	(–)	Renal disease in which filtration is impaired, oliguria, shock, anemia.
TmG,	(–)	Tubular damage, (TmG also reduced by obliteration of glomeruli), any extensive renal disease.
TmD		
PSP	(+)	Fever, diuresis.
PSP	(–)	Any extensive renal disease.
Dilution, Concentration—Reduced range—tubular damage by any extensive renal disease.		

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- Parathyroid extract, therapeutic test, *Sept*, 1248  
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Ammonia	(+) Pregnancy, toxemia of pregnancy, vomiting, diarrhea, dehydration, acidosis, urinary infection by urea-splitting organisms.
	(-) Renal insufficiency.
Total Reducing Substances	(+) Glycosuria in diabetes mellitus, Cushing's syndrome, renal diabetes, chronic or acute pancreatitis, pernicious anemia, pregnancy, severe pyogenic infection, pentosuria, lactosuria.
Ketones	(+) Alkalosis, starvation, prolonged vomiting, diarrhea, diabetes mellitus.
Sodium	(+) Diuresis, renal insufficiency, Addison's disease, after meals.
	(-) Sweating, renal insufficiency, diarrhea, vomiting, dehydration, anesthesia, pneumonia, diabetes mellitus, Cushing's syndrome, cardiac decompensation, nephrotic syndrome.
Potassium	(+) Diuresis, dietary increase, drugs, renal insufficiency, family periodic paralysis, Cushing's syndrome.
	(-) Addison's disease, renal insufficiency, dehydration.
Calcium	(+) Hyperparathyroidism, excess vitamin D intake, diuresis, acidosis.
	(-) Renal insufficiency, hypoparathyroidism, hyperthyroidism, steatorrhea, diarrhea, vitamin D deficiency.
Magnesium	(+) Acidosis.
	(-) Hyperphosphatemia, high fat intake, alkalosis, hyperparathyroidism.
Iron	(+) Hemachromatosis, hematuria, hemoglobinuria.
Chloride	(+) Renal insufficiency, diuresis, high chloride intake, acidosis, Addison's disease.
	(-) Starvation, dehydration, diarrhea, vomiting, after meals, sweating, prolonged hyperventilation, anesthesia, alkalosis, fever, cardiac decompensation, renal insufficiency, pernicious anemia, Cushing's syndrome.
Iodine	(+) Hyperthyroidism.
	(-) Hypothyroidism.
Sulfur	(+) Cystinuria, acute yellow atrophy, melanuria.
Ethereal Fraction	(+) Phenol ingestion, intestinal obstruction.
Phosphate	(+) Acidosis, hyperparathyroidism, hyperthyroidism, vomiting.
	(-) Hyperinsulinism, renal insufficiency, hypoparathyroidism, hypothyroidism, pregnancy, anesthesia.
Urinary Pigments—Porphyrins	(+) Acute porphyria, excess intake of veronal, sulfonal, etc., congenital porphyria, hepatic disease, pernicious anemia, hemolytic anemia, hemoglobinuria.
Vitamin	(-) Renal insufficiency and dietary deficiency.

## 6. RESPIRATORY DATA

### IN HEALTH

#### Blood Gases:

##### Arterial

Oxygen Content.....	16-20 vol. per cent	pO <sub>2</sub> 95-100 mm. Hg
Oxygen Hemoglobin Capacity...	17-21 vol. per cent	
Oxygen Content/Oxygen Capacity.....	95-97.4 per cent	
Carbon Dioxide Content.....	49.6-54.4 vol. per cent	pCO <sub>2</sub> 40.2-47.2 mm. Hg
Carbon Dioxide Content (T40) ..	48.3-52.9 vol. per cent	
Carbon Monoxide.....	0.1-0.5 vol. per cent	

##### Venous

Oxygen Content.....	11.0-16.9 vol. per cent	pO <sub>2</sub> 30-50 mm. Hg
Oxygen Content/Oxygen Capacity.....	60-35 per cent	
Carbon Dioxide Content.....	55-74 vol. per cent	pCO <sub>2</sub> 37-58 mm. Hg
Carbon Dioxide Content (T40) ..	43.3-55.9 vol. per cent	

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## 7. HEMATOLOGICAL DATA

## IN HEALTH

*Blood Cytology*

Total leukocytes.....	7,000-10,000 cells/cu. mm.
Myelocytes.....	0
Juvenile neutrophils.....	3-5 per cent
Segmented neutrophils.....	54-62 per cent
Eosinophils.....	1-3 per cent
Basophils.....	0-1 per cent
Lymphocytes.....	25-33 per cent
Monocytes.....	3-7 per cent
Platelets.....	250,000-400,000/cu. mm.
Red blood cells male.....	4,600,000-6,200,000 cells/cu. mm.
female.....	4,200,000-5,400,000 cells/cu. mm.
Reticulocytes.....	0-2 per cent
Hemoglobin male.....	14.0-18.0 gm. per 100 cc.
female.....	12.0-16.0 gm. per 100 cc.
Volume, packed cells (hematocrit) male.....	40.0-52.0 cc. per 100 cc.
female.....	37.0-47.0 cc. per 100 cc.
Mean Corpuscular Volume.....	82.0-92.0 c.μ.
Mean Corpuscular Hemoglobin.....	27.0-31.0 γγ
Mean Corpuscular Hemoglobin Concentration.....	32.0-36.0 per cent
Mean Corpuscular Diameter.....	7.2-7.8 μ
Erythrocyte Fragility Test	
Slight hemolysis.....in	0.45-0.39 per cent sodium chloride
Marked hemolysis.....in	0.42-0.36 per cent sodium chloride
Complete hemolysis.....in	0.33-0.30 per cent sodium chloride
Erythrocyte Sedimentation Rate	
Wintrobe.....	0-15 mm./hour
Westergren—male.....	1-3 mm./hour
female.....	3-7 mm./hour
Rourke-Ernstene.....	0.1-0.4 mm./min.
Bleeding Time.....	1-3 min.
Coagulation Time.....	2-10 min.
Retraction Time of Blood Clot.....	1 hour
Prothrombin Time (Quick).....	12-14 seconds (60-120 per cent of normal)
Capillary Fragility Test.....	10-15 petechiae/sq. in. on forearm, 5 cm. below elbow, after 10 min. cuff pressure on arm at 90 mm. Hg

*Bone Marrow Cytology*

Granulopoietic Series	Per Cent
Myeloblasts.....	0.3-5.0
Promyelocytes.....	1.0-8.0
Myelocytes—neutrophilic.....	5.0-19.0
eosinophilic.....	0.5-3.0
basophilic.....	0.0-0.5
Metamyelocytes ("juvenile forms").....	13.0-32.0
Polymorphonuclear neutrophils.....	7.0-30.0
eosinophils.....	0.5-4.0
basophils.....	0.0-0.7
Lymphocytes.....	3.0-17.0
Plasma cells.....	0.0-2.0
Monocytes.....	0.5-5.0
Reticulum cells.....	0.2-2.0
Megakaryocytes.....	0.03-3.0

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Myelocytes	(+)	Myelocytic leukemia, pernicious anemia, agranulocytosis.
Metamyelocytes	(+)	Agranulocytosis.
Polymorphonuclear Granulocytes	(+)	Leukemias.
	(-)	Pernicious anemia.
Lymphocytes	(+)	Lymphatic leukemia.
Plasma cells	(-)	Multiple myeloma.
Monocytes and Reticulum Cells	(+)	Monocytic leukemia.
Megakaryocytes	(+)	Polycythemia vera.
Pronormoblasts	(+)	Iron deficiency.
	(-)	Pernicious anemia.
Normoblasts	(+)	Iron deficiency, polycythemia vera.
	(-)	Pernicious anemia, aplastic anemia.
Megaloblasts	(+)	Markedly—pernicious anemia.

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## CONTRIBUTORS TO THIS NUMBER

Samuel Bellet, M D , Instructor in Medicine, School of Medicine, University of Pennsylvania, Associate in Cardiology, Graduate School of Medicine, University of Pennsylvania, Assistant Chief, Division of Cardiology, Philadelphia General Hospital

E Ruth Breitwieser, M D , Assistant Instructor in Medicine, School of Medicine, University of Pennsylvania

John J. Calarco, M D , Captain, Medical Corps, Army of the United States, Ward Officer, Medical Service, —th Station Hospital, Medical Inspector, U S Forces, Unit —

Thomas W. Clark, M D , Captain, Medical Corps, Army of the United States, Ward Officer, Medical Service, —th Station Hospital (Assistant Demonstrator in Medicine, Jefferson Medical College )

George M Coates, M D., F.A C S , Professor of Otorhinology, Graduate School of Medicine, University of Pennsylvania, Emeritus Professor, School of Medicine, University of Pennsylvania

Eric Denhoff, M D , Captain, Medical Corps, Army of the United States, Chief of the Laboratory Service, —th Station Hospital (Research Assistant, Emma Pendleton Bradley Home, East Providence, Rhode Island )

Garfield G Duncan, M D , F A C P., Colonel, Medical Corps, Army of the United States, formerly Medical Consultant, —th Army, now Chief of Medical Service, England General Hospital, Atlantic City, New Jersey (Chief of "B" Medical Service, Pennsylvania Hospital, Clinical Professor of Medicine, Jefferson Medical College )

Charles William Dunn, M D , F A C P , Assistant Professor of Medicine, Graduate School of Medicine, University of Pennsylvania

David Q. Ewing, M D , Major, Medical Corps, Army of the United States, Assistant Chief of Medical Service, —th Station Hospital (Assistant Physician, Pennsylvania Hospital )

Clark M Forcey, M D , Captain, Medical Corps, Army of the United States, Chief of the X-ray Service, —th Station Hospital

Harlan F Haines, M D , Captain, Medical Corps, Army of the United States, Ward Officer, Medical Service, —th Station Hospital (Assistant Physician, Pennsylvania Hospital, Philadelphia, Associate Chief of Medical Service, Delaware County Hospital )

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D. L. Turner, Ph.D , Research Chemist, Jefferson Medical College

Joseph B Vander Veer, M D , Lieutenant Colonel, Medical Corps, Army of the United States, Commanding Officer, formerly Chief of Medical Service, \_\_\_th Station Hospital, Chief Malariaologist, U S Forces, Unit \_\_\_ (Associate in Medicine, School of Medicine, University of Pennsylvania, Physician, Pennsylvania Hospital )

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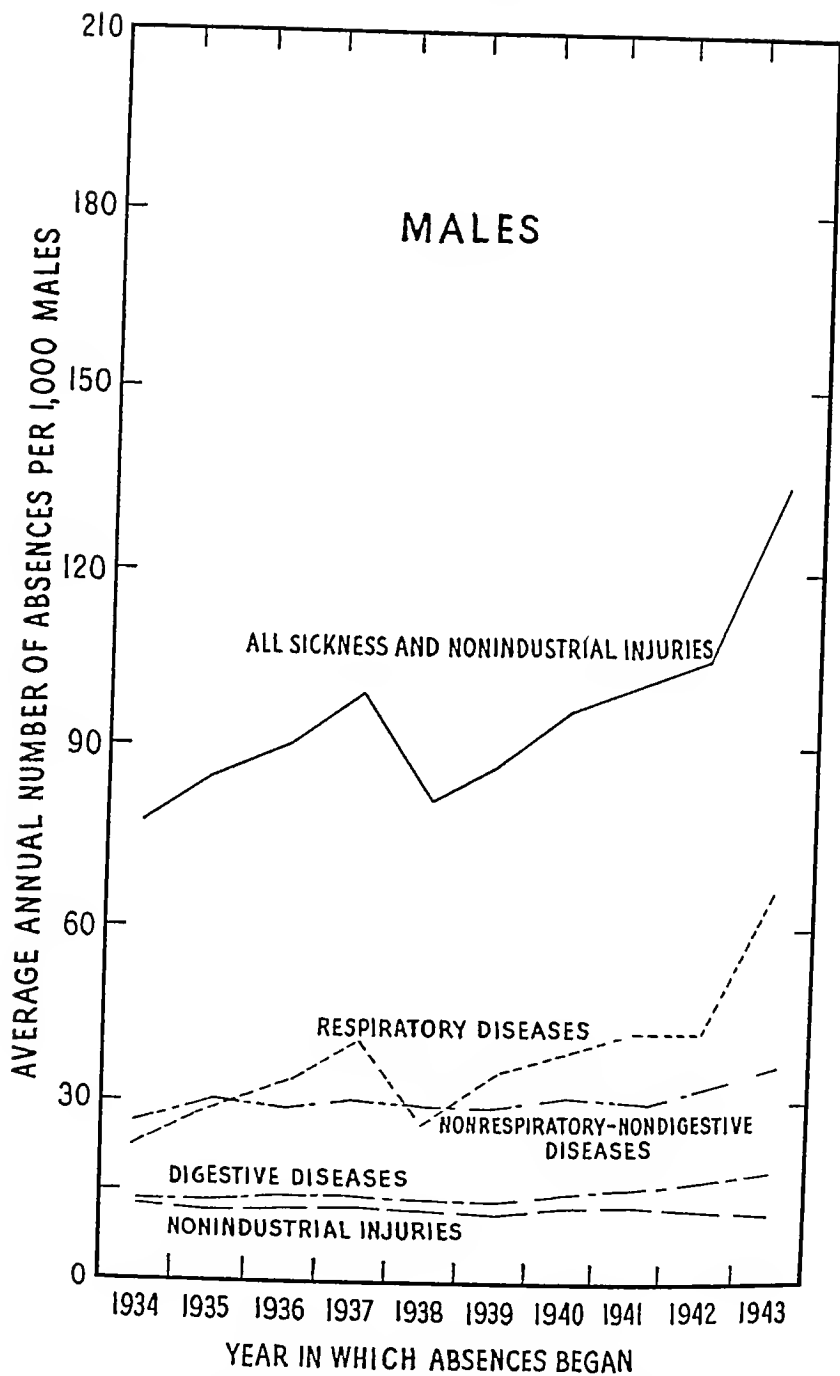


Fig 97—Average annual number of absences per 1000 males on account of sickness and nonindustrial injuries disabling for eight consecutive calendar days or longer, by broad cause group, variation of rates with time, experience of *male* employees in various industries, 1934-43, inclusive

by the U S Public Health Service <sup>19, 21</sup> Sickness absenteeism among males due to respiratory disease has shown a steadily mounting rate

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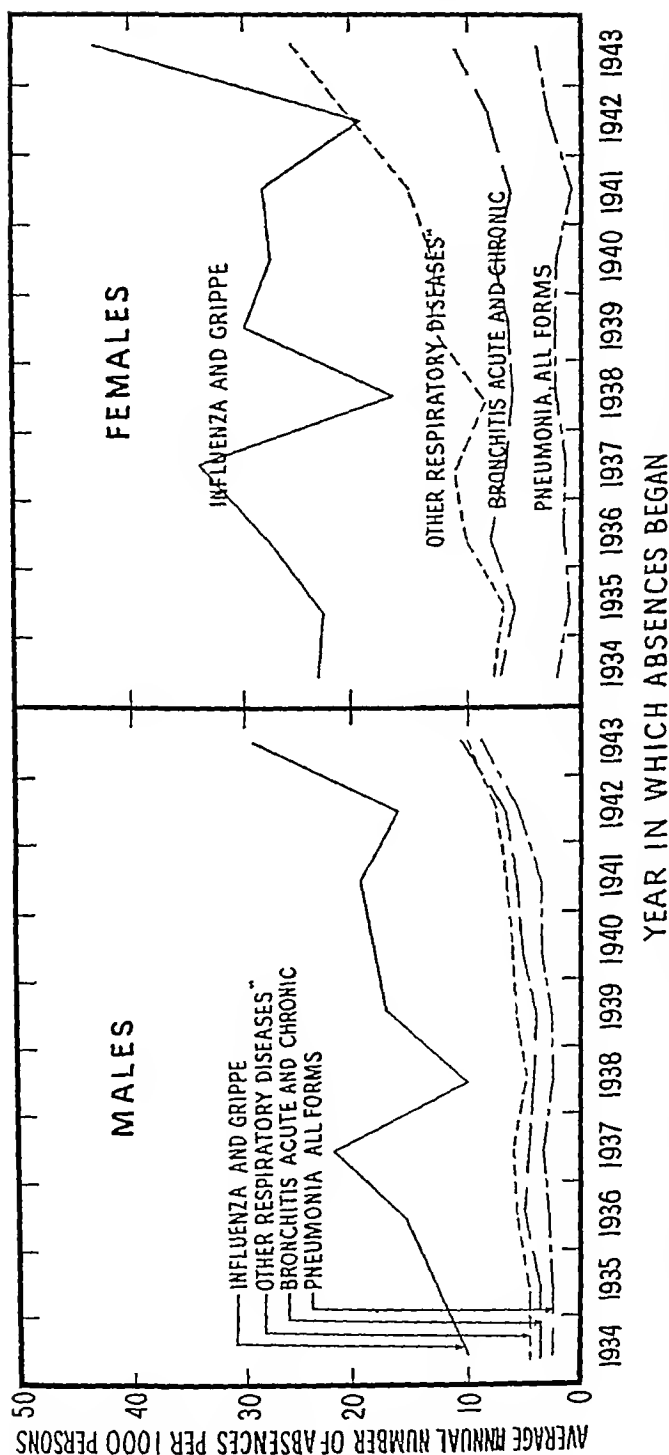


Fig 99—Average annual number of absences per 1000 persons on account of selected respiratory causes disabling for eight consecutive calendar days or longer, by sex, variation of rates with time, experience of *male* and *female* employees in various industries, 1934-43, inclusive

1939 through 1942 but at a high level. In 1943<sup>21</sup> there was further striking increase in frequency of the respiratory group of diseases, the male and female rates being 61 and 57 per cent in excess of the cor-

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in 1942 On the basis of 300 working days per year, this waste is approximately equivalent to the time of 470,000 persons working for a year

The Bureau of Labor Statistics publishes monthly data on straight-time hourly earnings for manufacturing industries in the United States as a whole<sup>7</sup> The author has computed an average daily earning by multiplying the straight-time hourly earnings (80.5 cents) by 8, the normal working day in American industry\* On this basis the loss in wages due to respiratory sickness amounted roughly to \$900,000,000 per annum This does not include the expenses for medical care, overhead expenses arising out of idle machinery and interruption in production schedules, and other items

The figures above are for 1942, it has already been indicated that respiratory disease rates in American industry in 1943 were even in excess of those in 1942<sup>41</sup> The average number of days lost from respiratory diseases in the above public utility during 1943 was for males 4.5 days and for females 6 days<sup>22</sup> The estimates for June, 1943, of the number of employed nonagricultural workers in the United States<sup>54</sup> were males, 28.6 million and females, 15.6 million Calculated on the same basis as above these data yield an approximate total of 128 million man-days and 93 million woman-days or over 220 million person-days lost to industry in the United States through respiratory disease in 1943, equivalent to a waste of the labor of about 740,000 persons working for a year The cost calculated as above would be almost 1.5 billion dollars

Although the desirability of ameliorating disease responsible for so great a wastage in time, money and well-being would seem to be self-evident, this desirability has been questioned, notably in the interesting volume on Air-Borne Infection by Dwight O'Hara,<sup>38</sup> from which we quote

From a sufficiently detached and objective point of view it is possible to look upon the present prevalence of respiratory infection with some satisfaction and equanimity, for it is more responsible than any other factor for keeping the population ready and resistant to that greatest cold-pandemic influenza—which might otherwise be a much more frequent and deadly visitor the writer prefers to think of them (the costs) as a reasonable price paid for the preservation of some semblance of respiratory resistance, for an initial resistance to invasion may be cheaper to maintain than to dispense with, biologically as well as socially and politically Let us not be too impatient with our yearly colds they keep us from becoming immunologically soft, as we assuredly do when we successfully isolate ourselves from them for any long period

\* It is unfortunate that daily rates of pay are not available Since the figure representing costs of time lost due to respiratory disease is at best only an approximate one the straight hourly earnings (excluding overtime earnings) are multiplied by 8 to secure a daily wage It is recognized that this is somewhat arbitrary





contrary to the long range trend 'If an effective resistance were purchasable at the price of frequent infection, this should automatically check the rise in infection rates. Infection rates on the contrary have continued upward even at an accelerating pace under conditions in the war years <sup>21</sup>

Carrying the thought further, it seems unlikely, too, that abolition of water sanitation or pasteurization of milk would be advocated on the grounds that these measures make us "immunologically soft" with respect to intestinal infection (although T E Lawrence in his *Seven Pillars of Wisdom* does smile at the expense of newcomers to Arabia because they cannot drink with impunity from desert water holes). Vaccination can keep the immunologic mechanisms in function, if necessary, more surely and more systematically than can haphazard natural infection.

"Sufficient unto the day is the evil thereof." The evils of respiratory infection are unequivocal, in the author's belief the means of dissemination of respiratory disease agents should be attacked whole-heartedly, uninhibited by concern over remote possibilities should we succeed beyond our hopes. In fact what is done in the next decades to understand and control air-borne infection may be taken as a significant index of how well we have learned one lesson of the war—that the broadest possible development of pure and applied science is fundamentally related to national security and well-being.

#### RELATIONSHIP BETWEEN RESPIRATORY DISEASE AND THE INFECTIOUSNESS OF AIR

Persons sneezing, coughing or even speaking loudly expel into the air large numbers of minute droplets which may contain in a viable and infective state any pathogenic bacteria or viruses present in their oral secretions. The larger of these potentially infectious droplets have a flight range of about a meter, they are conspicuous, are easily recoverable on bacteriological plates, and their ability to transmit respiratory infection is obvious. When droplets or sputa have dried on solid surfaces their residues may become the source of infective dust.

The role of droplets was notably stressed by the German hygienist Flugge\* in 1897,<sup>17</sup> and the doctrines of "droplet-infection" and dust-infection, or transmission of respiratory infection by droplets and by infective dust dominated thinking in regard to respiratory disease for thirty years.

The greater part of the potentially infective material expelled by persons into the air, however, is not contained in droplets visible without special means, but in smaller droplets which evaporate almost instantaneously. The basic experimental demonstration was made by

\* Actually, however, Flugge himself appreciated the importance of invisible droplets accompanying the coarser visible droplets, these, he recognized, may persist in air for hours and reach distant parts of enclosed spaces.

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Dr M W Jennison has kindly permitted reproduction of illustrative pictures Figure 100 shows, above, a violent, unstified sneeze recorded by the stroboscopic-light, high-speed photographic technic Many such



Fig 101—*Upper*, A sneeze through a mask of the type worn by some surgeons The mask was constructed of four thicknesses of muslin of 48 by 52 mesh *Lower*, A sneeze through a mask of the type worn by some surgeons The mask was constructed of four thicknesses of muslin of 50 by 56 mesh

photographs analyzed by Dr Jennison showed in each sneeze about 20,000 droplets, ranging in size from about  $10\ \mu$  to about  $400\ \mu$ , between 40 and 80 per cent of these droplets were estimated to have

# GYNECOLOGIC EXAMINATION—PREMARITAL COUNSEL

ROBERT C. McELROY, M.D.

AN introduction to gynecic treatises and study must, of necessity, be concerned with examination of the patient. It is assumed that adequate basic training in the fundamental embryology, anatomy, histology and pathology as related to this field has been acquired.

Gynecologic examination is as integral a part of the armamentarium of the general practitioner as it is to the specialist. The great differences in the approach of the two types of practitioner lie in the allotment of the facts in the history taking, time and facility for examination, systematic approach and thoroughness. Errors in diagnosis are due to the sins of omission rather than commission.

Preliminary preparation of the patient for examination requires that the bladder be emptied immediately prior to examination. The rectum should be emptied and enemas utilized when necessary. All constrictive clothing and supportive garments should be removed. Confidence and cooperation of the patient will facilitate matters to the utmost. Gentleness and tact combined with reassurance will mentally prepare the patient for an examination that notoriously carries a stigma of pain and embarrassment. The presence of a nurse, assistant or some third disinterested party serves as protection to the physician but offers little benefit to the patient beyond moral support.

## HISTORY

History taking is a necessary preface to any physical examination. Facts common to all medical history of either specialized or general nature must be noted to cover general and systemic etiologic factors of pelvic disease. Certain facts pertinent to the female in respect to her age, color and marital state (past and present) must be noted. An accurate menstrual history covering age of onset; type of flow, whether regular or irregular; interval; duration and quantity of flow (number of napkins); the character, whether accompanied by clots or passage of tissue; color; odor; association of pain, its location, radiation and character, time in relation to flow; the date of the last menstruation, both normal and abnormal, and finally menopausal symptoms, if the latter be present, must be recorded. Childbearing being responsible for or related to complaints, demands that an accurate obstetrical history include the number of labors and abortions; their respective dates, character and the method of termination; the duration of the puerperia

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\* Instructor, Department of Obstetrics and Gynecology, School of Medicine, University of Pennsylvania; Assistant Obstetrician and Gynecologist, Philadelphia Lying-in, University of Pennsylvania and Philadelphia General Hospitals.

diameters less than  $100\ \mu$  and hence to be of the size which evaporate in the air to form potentially infective "droplet-nuclei" Figures 100,



Fig 103—*Upper*, Droplets sprayed into the air from a cough Only a few droplets are produced in a cough as compared with the thousands produced in a sneeze *Lower*, Enunciating the letter F Consonants are more difficult than vowels to pronounce without forming droplets The droplets produced in speaking are larger and fewer than those from sneezing

lower, and 101 are photographs of sneezes through surgical masks of increasingly fine mesh and hence increasing efficiency in screening

## GYNECOLOGIC EXAMINATION

**Equipment.**—The instruments for gynecologic examination are not numerous but they must be specially adapted to suit the needs of the field. The examining table should be one of adjustable length with the facility to elevate the head and shoulders. The supports for the extremities may utilize either heel rests or leg holders. The covering mattress should be firm, smooth yet comfortable. Drawer space at the foot should contain the equipment to be mentioned below.

Lighting facility should be either a no-spot lamp, head mirror or light, or a speculum light. The ordinary goose-neck is awkward and burns the patient and the operator while obstructing the view.

The remainder of the equipment includes rubber gloves, lubricant, various types and sizes of specula, tenacula, dressing forceps, steel or glass catheter, suction curette, dilators, sounds, probes, biopsy forceps, cautery or electro coagulation apparatus, pressometer or Rubin apparatus, microscope, needles and syringes, sterilizer, diaphragm rings, solutions, blood counting apparatus and pessaries.

**Position of the Patient.**—The gynecology examination necessitates a variance in position of the patient to secure completeness and accuracy. The recumbent, dorsal lithotomy, Sims', knee-chest and Trendelenburg positions all have peculiar usefulness. Abdominal examination is best in the recumbent; bimanual examination by the dorsal lithotomy; Sims' and knee-chest for fistulas or uterine replacement.

**The Examination.**—Proper positioning with adequate coverage to prevent undue exposure is the correct approach to examination. *Abdominal examination* precedes pelvic examination. Tumor masses, tympanites, ascites, rigidity and tenderness as well as peristaltic activity are noted. Tumor masses may be smooth or irregular, firm or elastic and do not produce distention of the flanks. Ascites show a fluid wave, shifting dullness and dullness in the flanks. Tympanites causes uniform distention with the characteristic high-pitched note on percussion. The presence of fetal parts and heart sounds makes pregnancy an easier diagnosis. Rigidity of the abdomen or absence of peristalsis indicates some inflammatory lesion and may be secondary to a pelvic lesion or a complication of it. Tumor masses caused by the urinary bladder may be dispelled by the catheter. Coronal tympany is present in ovarian cysts.

On completion of the abdominal examination the *pelvic examination* is next in order. It is carried out with the gloved hand to protect the operator and to respect the aesthetic sense of the patient. One or both hands may be used depending on the ability to completely explore the pelvis. The patient is cautioned that the examination is discomforting but not painful and she may expedite matters by relaxation and deep breathing.

Fundamentally, the exploration can be accomplished thoroughly by means of the internal and external hands to exert counterpressure. The

micro-organisms may occur in clusters, each cluster is counted as one colony in the impinging devices but the clumps are more or less broken up in the atomizing devices. The authors recommend that

Information on the manner in which micro-organisms occur in a certain airspace should therefore cover the following points

- 1 The total number of organisms present whether occurring singly or in clusters. An approximation to this number is given by the atomizing devices.

- 2 The number of particles or droplet nuclei, which contain micro-organisms, either singly or in clusters, and which remain suspended in the air or are in the process of settling. This number is approximated by the impinging devices.

- 3 The number of particles or droplet nuclei, containing micro-organisms, which are heavy enough to settle through gravity. The open plate method supplies this information.

### CONTINUOUS DISINFECTION OF AIR

Effective continuous disinfection of the air of enclosed spaces has already been shown to be practicable where conditions are favorable and where the problem is approached with adequate determination and technical facilities and skill. The practical means are physical (ultraviolet radiation,<sup>57</sup> dust suppressive measures<sup>55</sup>) and chemical (germicidal vapors). Doubtless physical and chemical means will each find appropriate place as mutually complementary measures in the fully matured art of providing noninfectious air in our future homes, transport vehicles and places of work and recreation.

**Ultraviolet Radiation**—Application of ultraviolet radiation to disinfection of air has been systematically reviewed in the American Association for the Advancement of Science volume on *Aerobiology*. The physiological and the germicidal effects of ultraviolet radiation, and the characteristics and standardization of commercially available ultraviolet sources are presented in detail. Successful application of ultraviolet radiation to reduction of wound infections in the operating room are presented by Dr. Deryl Hart, the pioneer in this field, and by Drs. Kraissl and Wilson of Columbia. Cross-infections in hospital wards and in children's nurseries and schools are reviewed and analyzed, and success in reduction of these cross-infections by appropriate use of ultraviolet irradiation is recorded. More detailed analyses of successful control of childhood contagions in schools have been published by Wells, Wells and Wilder,<sup>58</sup> and by Wells and Wells.<sup>59</sup>

More recent records of germicidal action against bacteria and viruses by ultraviolet radiation in a children's hospital, with reduction in cross-infection, have been published by Robertson, Doyle and Tisdale,<sup>43</sup> by Sommer and Stokes,<sup>48</sup> and Henle, Sommer and Stokes.<sup>26</sup> The Council on Physical Therapy of the American Medical Association has found ultraviolet lamps acceptable as an adjuvant in the disinfection of air,<sup>10</sup> and commercially available burners and fixtures of several types have

hesions. The uterine mass is differentiated from other pelvic masses by demarcation or sounding.

The uterine ligaments are not easily felt, but the round ligaments may be palpated as a cordlike mass arising from the cornua. The uterosacral ligaments are felt in the cul-de-sac and are best noted in pelvic endometriosis or spreading carcinoma.

Examination of the adnexa requires skill and experience. They are motile for great distances in almost any direction and tend to slide away from the exploring hands. The normal tube cannot be palpated but enlargements due to ectopic pregnancy, salpingitis, pyosalpinx or hydrosalpinx can be felt. An ectopic gestation is exquisitely tender while the other conditions show variations in shape and a lesser degree of tenderness. The ovary can be palpated, but must be trapped between the abdominal or vaginal hands as well as the lateral pelvic wall. It must, therefore, be scooped into this site. The ovary has a sensitivity similar to that of the testicle and pressure upon it may produce nausea or vertigo. Cysts have the characteristic elastic feel, except the dermoid, which is stony hard and located anterior to the broad ligament. They are freely motile usually, while the parovarian cyst is in close approximation to the uterus and is fixed. Free motility may cause confusion with a pedunculated fibroid. The small cysts are retention in type while the large ones are proliferative.

Completeness demands that the bladder and ureters be palpated for masses or tenderness. During the palpation of the latter the uterine arteries may be felt in the lateral fornices.

It is truly said the gynecologists make no rectal examinations and the surgeon fails to utilize the vagina. The rectum affords an additional portal of entry especially in the virgin or to determine the state of the rectovaginal septum in abscess or endometriosis. Rectal tenderness is prominent in appendicitis.

*Instrumentation* gives further conclusive evidence by exposure of the vagina and cervix with the speculum. Uterine replacement may be accomplished by traction on the cervix with the vulsellum. The uterine sound shows the direction and depth of the endometrial cavity and if bleeding is encountered is helpful in the Clark test for fundal carcinoma. Intracavity tumors may be felt by this method. Before sounding the uterus the date of the last menstruation must be known in order not to produce an abortion, frequently the reason a patient consults the physician. The fine probe will locate fistulas or sinus tracts. The biopsy forceps should be wisely employed to determine the histopathology of suspicious lesions. Insensitiveness of the cervix to manipulation except dilatation affords opportunity for the painless application of cauterization and coagulation procedures to erosions and ectropions. Marked superficial vascularity, however, contraindicates cauterization because of the possibility of additional uncontrollable bleeding. Intrapelvic infection may be activated by such a procedure.



tion to the problem of disinfecting the air of industrial plants, offices, assembly halls, railroad cars and similar places. It emphasizes, however, that the specifications of engineering design and other features determining the adequacy and safety of the practical art must be further developed and applied before evaluation will become possible.

Another paragraph of the Council's statement discusses responsibility for design of installations.

It is to be noted that a lamp used for disinfecting purposes is a single unit in an installation, and that compliance of the ultra-violet output of a single lamp unit with the Council's requirements does not insure adequate radiant disinfection or the safety of the occupants of the room in which an installation of such lamps is in actual use. Obviously the manufacturer and distributor of such lamps must assume some responsibility for the adequacy of the lamp installation for purposes of radiant disinfection of the air and for the adequacy of the protection from injury of the occupants of the space irradiated. Concerning these questions the Council cannot undertake supervision or assume responsibility for the satisfactory performance of any particular installation.

The Senior Biophysicist of the Division of Industrial Hygiene, National Institute of Health (who also is Associate Referee for the American Public Health Association on Disinfection of Air by Ultra-violet Irradiation)<sup>20a</sup> has critically reviewed applications, precautions and limitations of the use of ultraviolet irradiation to disinfection of air.<sup>20</sup> The statement of the Council on Physical Therapy is quoted with approval. "Obviously the manufacturer and distributor of such lamps must assume some responsibility for the adequacy of the lamp installation for purposes of radiant disinfection of the air, and for the adequacy of the protection from injury of the occupants of the space irradiated."

Acceptance by the architectural and engineering groups in whose province air hygiene may be considered as properly falling, of a measure of responsibility for elaborating specifications for proper design and servicing of installations would be an important step toward development of a practical art of air hygiene.

The efficacy of ultraviolet irradiation in killing air-borne bacteria and viruses under conditions in which the air is relatively free from dust and lint has been confirmed in Great Britain by Andrewes and others<sup>2</sup> and by Edward, Lush, and Bourdillon.<sup>10</sup> The difficulty of disinfecting dust-laden air by this means has also been emphasized. Andrewes and his co-workers suggest the combination of air filtration and ultraviolet irradiation in recirculation systems and for certain special purposes.

Complete success in controlling the spread of a specific air-borne disease under rigid experimental conditions has recently been recorded by Lurie.<sup>34a</sup> A rabbit population, 73 per cent of whose unprotected control animals developed progressive tuberculosis, was completely

the considerations. The entire field could only be covered thoroughly by successive consultation with the physician, psychiatrist and marriage counselor.

Consultation with the physician is on an intimate and personal relationship which must be handled with the greatest tact and gentleness. A short but pertinent history of previous illness should be combined with the examination, which should be general as well as pelvic. The physician should bring to light certain definite attitudes, entrenched shames, inhibitions, ignorances and erogenous practices in order to disperse these and possibly aid the groom in his approach and ability to stimulate his bride. Anatomic abnormalities should be noted and, if a tight hymen is present, it should be dilated or stretched with or without the aid of anesthesia and with full consent of both bride and groom. This may be accomplished in several ways. Instruction in douching will serve to dilate the orifice and accustom the vagina to a foreign body. The patient may do the dilation by using her finger or thumb at repeated intervals to enlarge the opening. The physician can accomplish it by slow, forceful dilation without anesthesia and tearing of the hymen. If necessary anesthesia is employed. When dilation is done, the woman can be assured that her first coitus will not be painful or unpleasant.

In the case of the woman who has had unpleasant experiences or who masturbates, assurance can be given that these practices have not harmed her. Such erogenous practices may give an index of stimulation points valuable in reaching a climax later on and the knowledge is passed on to the male as advice without revealing its source. Variant positions should be known and described for satisfactory intercourse. She should be instructed to accept and cooperate with her husband's caresses and to guide him where necessary. The marital act is not a duty or chore simply to be tolerated because marriage vows have been spoken. It is indulged in for expression of love and affection and the pleasure derived therefrom. Simultaneous climax can be reached if sufficient practice is had and the proper areas stimulated. Actual insertion of the phallus should not occur until the female climax is near in cases of premature ejaculation. If this is very premature, urologic advice is recommended. Coitus during the menses is not harmful and may be more satisfactory because of the increase in the sex response at that time. A small douche will remove the messy character of the act. A complete knowledge of contraceptive control is fundamental and the method best suited to the couple advised. The diaphragm is most efficient and where this cannot be fitted, the condom is used until the hymen is dilated to permit the use of a diaphragm. In cases of religious scruples the Ogino-Knaus method of rhythm control is advised. Pregnancy should not be delayed too long since it will complete the final union of the family and serve to cement the marriage.

Edward and Lidwell<sup>15</sup> report favorable tests on sterilization of air-borne influenza virus with hypochlorous acid gas

A concentration of 1 vol of gas in 2 million vol of air is probably effective in destroying 99 per cent or more of virus particles when the proportion of these in the air is small. Preliminary experiments on mice and cats are recorded which failed to reveal any toxic effects produced by inhaling the gas in relatively high concentrations or for prolonged periods. Acute irritation of mucous membranes only was found. This did not appear to lead to any increased susceptibility of mice to subsequent infection with influenza.

Exploration of the possibilities of continuous disinfection of air by chemical substances has made and is making rapid progress in America through the work of O. H. Robertson and his associates. They determined that certain of the glycols alone, notably propylene glycol<sup>44</sup> and triethylene glycol<sup>45</sup> provided promising means for continuous disinfection of air. They demonstrated that the germicidal action depended, not, as earlier supposed, upon collision of fluid droplets with air-borne bacteria, but upon condensation of hygroscopic glycol molecules upon air-borne droplets containing bacteria. One gram of propylene glycol dispersed as vapor in 5 or 10 million ml of air and 1 gm of triethylene glycol vapor in several hundred million ml of air was found to kill pathogenic respiratory bacteria and the virus of influenza in air in seconds or minutes. Rat and monkey colonies kept constantly in atmospheres saturated with vapors of propylene glycol for periods up to eighteen months, and triethylene glycol up to a year suffered no ill effects detectable by observation or microscopic examination.<sup>46</sup> As Robertson says

The germicidal activity of glycol vapors is markedly influenced by certain environmental factors, the most important of which is atmospheric humidity. A dry atmosphere is unfavorable. Likewise desiccated bacterial particles are not as susceptible to the vapor action as are moist ones. It has been found that the glycols are most effective at relative humidities between 40 and 60 per cent.

Subsequent work by Bigg, Jennings and Fried<sup>3</sup> places the relative humidity for maximal germicidal action of glycol vapors at from 30 to 50 per cent. These papers<sup>3-5</sup> indicate the types of apparatus that are being developed for disinfection of the air of large enclosed places by glycol vapors.

Careful investigation of the possibility of fire hazard resulting from the dispersal of glycol vapors into the atmosphere of enclosed spaces has also been made by Bigg, Jennings and Fried.<sup>4</sup> These authors conclude

In the vapor-phase concentration required for air sterilization, propylene and triethylene glycol offer absolutely no fire or explosive hazard. The addition of water to these substances greatly reduces the possible fire hazard produced by their presence in storage or vaporizing devices.

difficult time than others in harmonizing their sexual relations because they are afraid to admit ignorance of the subject and will go to any end to solve the problem themselves before seeking advice. They, too, have more consideration for each other and when a problem exists they will make an attempt at a solution. If this fails they will practice continence or indulge only to satisfy their partner. The lower income groups rarely have these difficulties and certainly they infrequently ask advice. With the existing means of recreation they are able to secure sufficient exercise and are not leading a pace that is killing. They do not, as a rule, take into consideration the financial burden of pregnancy and rarely deny themselves because of an inability to provide a college education for the offspring. It is not intended to imply that they have less consideration for each other but that they more frequently enter into the act for sheer expression and pleasure. They have their problems, nevertheless, and premarital advice should always be available to them and should be offered without being rude.

The physician must preserve dignity and abstain from levity during all of the discussion. He must maintain a sympathetic and helpful attitude. He will remember that through education we can teach success in marriage and parenthood by enlisting effort, courage and intelligence, thus preventing the disastrous terminations of so many marriages in the divorce court. He can promote a new outlook on a problem that deserves more careful consideration than has been given it.

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In the case of tri-ethylene glycol the maintenance of a satisfactory concentration presented a greater problem, because of the narrow range between bactericidal concentration and precipitating concentration mentioned above. In the absence of sensitive methods for regulating or measuring concentrations of tri-ethylene glycol vapor in air, a rate of vaporization sufficient to disinfect the air to a considerable degree was often found to produce precipitation of glycol on windows, floors and objects in the ward. The concentration of this vapor in air ranged between 0.0018 mg/liter and 0.0033 mg/liter.

The difficulties encountered in this study in the use of tri-ethylene glycol are due largely to the early stage of engineering development of the field, and to the relatively small size of the enclosed spaces involved. In a larger volume of air the fluctuations in glycol concentration caused by occasional opening of doors, etc., would be proportionately smaller and the concentration could be maintained in a narrower range. The ultimate development of devices to regulate the rate of vaporization of tri-ethylene glycol by the concentration of the vapor present in air at the moment may obviate the difficulties in using this disinfectant and permit workers to take advantage of its higher potency.

At the present writing, however, it would appear that in the absence of refined devices to regulate the rate of vaporization of glycol, propylene glycol is the agent of choice in small wards, offices and spaces of similar size.

In his report as Associate Referee on Disinfection of Air by Germicidal Vapors and Mists,<sup>42</sup> Professor O. H. Robertson writes

Practical application of the use of glycol vapors for the purpose of controlling air-borne infection has had to await the construction of suitable apparatus for the dispersion of glycol vapors into large enclosed spaces and the development of an instrument to control automatically the concentration of glycol vapor in the air. Rapid progress is being made in the solution of both these problems.

Types of vaporizing devices for large spaces,<sup>47</sup> for smaller spaces<sup>50</sup> and means for the regulation of vapor concentration<sup>47</sup> are in process of elaboration and trial.

**Dust-suppressive Measures**—Consideration of the air as a vehicle of infection would be very incomplete without reference to the importance of dust, both as a carrier of pathogenic bacteria and viruses and as a shield of air-borne pathogens against the means used for disinfection of air, such as ultraviolet radiation and germicidal vapors. British investigators<sup>55</sup> in particular, working under wartime conditions, have found dust a very serious obstacle to application of measures for disinfection of air. They have introduced practical methods for reducing dust from floors, textiles and bedclothes by treatment with light paraffin oils.

Results of practical trials of the effect of suppression of dust by *oiling* have recently been recorded.<sup>60</sup> Measles, a catarrhal disease, often complicated by hemolytic streptococcal infection, affords conditions

# ADVANCES IN THE TREATMENT OF VAGINITIS

A. E. RAKOFF, M.D.\*

PROGRESS in the treatment of vaginal infections and associated disorders of the vagina during the past several years has resulted from a better understanding of the biology and physiology of the vagina in health and disease as well as from the introduction of new chemotherapeutic drugs, antibiotics and hormonal preparations. Also of importance has been the improvement in the technics of applying medications to the vagina particularly with regard to the development of medications which could be effectively distributed over the entire lower genital tract and of the proper physical and chemical character to mix intimately with the vaginal and cervical secretions.<sup>1</sup>

## BIOLOGY OF THE NORMAL VAGINA

The effective treatment of infections and discharges of the vagina requires an appreciation of the mechanism by which the normal biologic characteristics of the vagina are maintained.<sup>2</sup>

The vaginal mucosa is under the direct influence of the ovarian hormones. The estrogens are the dominant factor in stimulating proliferation of the vaginal epithelium and thus maintaining a vaginal mucosa of normal thickness. The estrogens are also responsible for the deposition of glycogen in high concentration in the vaginal epithelium; progesterone may aid in this process, while androgens inhibit both proliferation and glycogen deposition. By the combined action of enzymes and bacteria the glycogen of the vaginal epithelium is metabolized and broken down to lactic acid. The resulting acidity of the vagina favors the growth of certain acidophilic bacteria, particularly the lactobacilli of Döderlein. These organisms tend to further increase the acidity of the vagina by utilizing glycogen and the carbohydrates resulting from the enzymatic breakdown of glycogen. The resulting pH of the vaginal secretion thus tends to become stabilized at 4.0 to 5.0 in the normal adult during the period of active ovarian function. Since very few other organisms can thrive in so acid an environment, Döderlein's bacilli quite commonly become established in practically pure culture in the normal vaginal tract. By this mechanism the genital tract is protected from exogenous infection.

In phases of diminished ovarian function such as in childhood, in the immediate postpartum period and in the postmenopausal years the diminished elaboration of estrogenic hormones produces a vaginal mucosa that is of diminished thickness, with little or no glycogen content and a less acid or even alkaline secretion ranging from pH 5.0 to 8.0. Under these latter circumstances Döderlein's bacilli tend to disappear from the vaginal secretion. The presence or absence of the lactobacilli is thus largely dependent upon the vaginal acidity. Almost all patients with a vaginal flora of Döderlein's bacilli alone (so called Grade I vaginal flora) have a vaginal pH ranging from 3.9 to 5.0. The majority of patients with a

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From the Departments of Obstetrics and Gynecology, Jefferson Medical College and Hospital, Philadelphia.

\* Assistant Demonstrator in Obstetrics, Instructor in Gynecology, Jefferson Medical College. Director of the Endocrine Laboratories, Jefferson Hospital.

making, the predominant strain being Type 6. Thus oiling of floors alone was not sufficient to control the spread of dust-borne haemolytic streptococci in measles wards.

In the *Test Ward*, while the full anti-dust measures of oiled bed-clothes, garments, etc., and oiled floor were in force (a) the mean haemolytic streptococcus count in the air during bed-making was reduced by 97.5%, (b) the mean bacterial count in the air during bed-making was 91% less, and the mean haemolytic streptococcus count 98% less, than in the *Control Ward*, (c) the mean bacterial count in the air during sweeping was 92% less, and the mean haemolytic streptococcus count 99% less, than in the *Control Ward*, (d) the Type 6 cross-infection rate was 18.6%, while in the *Control Ward* it rose to 73.3%, (e) the middle-ear complication rate due to Type 6 was 2.8%, compared with 14.3% in the *Control Ward*. Thus the oiling of all bed-clothes and ward-linen, in addition to the oiling of floors, effectively controlled dust-borne streptococcal infection in measles wards. Cross-infection from direct contact or mediate means was not prevented by anti-dust measures.

A high streptococcal infection rate occurred in spite of intensive sulphonamide prophylaxis. The cross-infecting Type 6 strain was found by *in vitro* tests to be sulphonamide-resistant.

A complete and practical technic for the application of dust-laying oils to blankets, sheets and other woolen and cotton fabrics has been worked out in the laboratories of the British Launderer's Research Association.<sup>25</sup>

In another British study<sup>1</sup> the wooden floors of all barrack rooms, sleeping huts, offices and lecture rooms in a military training center were treated with spindle oil at regular intervals. The floors of a similar unit were left untreated as a control. Careful weekly records were kept of all men reporting sick with a respiratory infection during the seventeen weeks ending March 27, 1943. The respiratory infection rate was 7 per 1000 men in the unit with oiled floors, 38 per 1000 in the control unit. The oil used was noninflammable, caused no unpleasant smell and made the floors easier to keep clean. "The regimental officers and men welcomed the oiling of the floors."

Experiments on the reduction of the infectivity of dust by floor irradiation with *ultraviolet* have been instituted by Hollaender, du Buy, Ingraham and Wheeler.<sup>30</sup> As a result of these experiments they suggest that "floor irradiation be combined with ceiling irradiation in practical tests in barracks or hospital wards to determine the effect of any ultraviolet irradiation in lowering morbidity rates or preventing cross-infection." They caution that "if such experiments be attempted it must be borne in mind that certain types of flooring may prove to be capable of reflecting sufficient amounts of ultraviolet to cause harmful effects."

Thus rationale and scientific basis have already been laid down for three independent types of measure for controlling the dissemination

Much more satisfactory than the acid douche is the use of a water-dispersable acid vaginal jelly\* which can be introduced into the vagina once or twice daily and which remains in contact with the vaginal mucosa over a prolonged period of time and thus more effectively creates a suitable acid medium.<sup>4, 5, 6</sup> A very satisfactory preparation\* consists of acetic acid, oxyquinoline sulfate, ricinoleic acid, boric acid and glycerine in a suitable vehicle. This jelly may be introduced at bedtime by the use of a special vaginal applicator containing 5 cc., which is followed in the morning by a simple acid douche. Persistent use of the vaginal jelly for several weeks generally leads to restoration of the normal vaginal flora which tends to persist provided any other underlying factors have been corrected.

#### ATROPHIC VAGINITIS

In the presence of a marked ovarian deficiency the vaginal mucosa may atrophy to a thin tissue-paperlike structure consisting of only a few layers of cells. Because of the susceptibility of this thin tissue to trauma and because of the associated decrease in vaginal acidity, inflammation, ulceration and infection readily result.

This type of condition can be readily corrected by administering estrogenic hormones in sufficient amount to cause proliferation of the vaginal epithelium and by treating the associated nonspecific infection by the methods already prescribed. A much more specific and rapid cure can be effected by applying the estrogenic hormone locally to the vaginal mucosa. This can be accomplished by the use of vaginal suppositories containing natural and synthetic estrogens or even better we have found the use of a water-dispersable acid jelly containing stilbestrol† in concentration of 0.5 mg. per cc. Five cubic centimeters of this jelly can be introduced nightly into the vagina by means of a special applicator and followed the next morning with a simple acid douche. By applying the hormone to the vagina locally intense cornification can be rapidly induced without producing excessive systemic effects of hyperestrogenism. After initial cure has been obtained the jelly may be used once or twice weekly as required to maintain a healthy vaginal mucosa.

#### POSTPARTUM VAGINITIS

A nonspecific vaginitis frequently occurs in the postpartum period because of trauma from delivery, the bathing of the vaginal mucosa with the alkaline secretions from the uterus and cervix, and because the vaginal mucosa has become thin and glycogen-poor in this phase of diminished ovarian function. This type of infection responds quickly to an acid vaginal jelly and acid douches. Even more satisfactory is the

\* Aci-Jel supplied by Ortho Pharmaceutical Corp., Linden, New Jersey.

† Generously supplied to us for investigational use as "Gynecological Cream" by Ortho Pharmaceutical Corp., Linden, New Jersey.



much is it worth in peacetime to reduce a corresponding loss of efficiency and well-being from the drain of respiratory infection?

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difficult and prolonged. The trichomonads can be readily killed in the laboratory by simple drying or by exposing them to relatively low concentrations of a great many antiseptics or common laboratory reagents.<sup>9</sup> Even in the vagina the organisms are rapidly destroyed on contact with a great many therapeutic agents. Unfortunately, however, occasional organisms can "hide out" in folds of tissue in the vagina or introitus, in the cervical canal, in the cervical glands, in the urethra<sup>10</sup> and Skene's glands, in the bladder and in Bartholin's glands. Within twenty-four to forty-eight hours after local treatment it is not at all uncommon to again find large numbers of the flagellates in the vaginal tract. Unfortunately it is not possible to reach these occasional organisms which are responsible for reinfestation by systemic chemotherapy. Sulfonamides given by mouth in adequate dosage and penicillin given by injection fail to destroy the organisms. It is, therefore, my studied opinion that the technic of treatment in these resistant cases is often far more important than the drug employed.

Symptomatic relief in almost all cases can be readily obtained by douching persistently twice daily with a simple acid douche, but only rarely will this effect a cure. Even the use of medicated douches containing permanganate, iodine, mercurials or other antiseptic is of no additional help in permanently eradicating the flagellates.

The use of acid vaginal jellies likewise affords symptomatic relief and persistent, twice-daily use cures some of the milder cases.

Sulfonamide jellies when used persistently will effect cures in perhaps a somewhat greater percentage of patients but in our experience have not been useful for the more resistant cases. The sulfonamide jellies are helpful particularly as an adjunct in those cases in which there are associated streptococcal infections. The sulfonamides per se are not highly trichomonadicidal.

Medicated suppositories are generally not as effective as the medicated jellies since they do not diffuse as effectively and frequently do not mix well with the vaginal secretions.

For local treatment of the vagina no technic works as well as the introduction of the drug to be used in powder form diluted with a drying base such as kaolin. Many such preparations are available including arsenicals such as aldarson, acetarson and carbarsone, silver picrate, argyrol, mercurials, sulfanomides and numerous other antiseptics. Although I have a preference for the pentavalent arsenicals, particularly aldarson,<sup>11</sup> I have been able to obtain satisfactory results with a considerable number of the antiseptic powders diluted with kaolin if the method of treatment has been appropriate.

The essentials of obtaining a cure involve thoroughness, frequency and persistence of treatment. The entire vaginal tract should first be cleansed with saline, 5 per cent sodium bicarbonate or suspensions of kaolin to remove all secretion and mucus. Particular care should be given to the cleansing of the cervix and introitus and any folds or

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jelly and an acid douche which is used for several months on days when insufflations are not given. Another problem which sometimes complicates the treatment of some severe cases of *Trichomonas vaginitis* is marked sensitivity of the patient to many drugs. This is sometimes a true allergy but more often the sensitivity is due to the extreme inflammation of the parts. Severe burning, irritation and edema may occur in such individuals after treatment. In this event treatment for the next several days should consist of simple saline douches every few hours, and cold compresses to the labia. After the acute inflammation has subsided insufflations with kaolin alone should be started, and then small increasing amounts of drug gradually added at each treatment.

#### VAGINAL MONILIASIS

Infections of the vagina with monilia and related yeastlike fungi have received considerable attention in the past several years. The infection produces a vulvovaginitis which gives rise to severe itching of the parts often with swelling of the labia and dermatitis of the surrounding skin areas. The discharge is not profuse but has a characteristic thick, cheesy consistency. The vaginal mucosa is generally coated with "thrush" patches. The infection is quite common during pregnancy, occurring in as many as 10 per cent in some prenatal clinics, but it is much less frequent in nonpregnant women. It also has a tendency to occur quite commonly among diabetic women. A high carbohydrate content and increased vaginal acidity favor the growth of the yeastlike fungi, thus explaining the increased frequency in pregnancy and among diabetics. In pregnant women infection may be transmitted to the baby at the time of delivery, thus giving rise to "thrush" in the newborn. Infection of the nipples of lactating women is also occasionally observed.

Moniliasis is a persistent infection and difficult to cure particularly in pregnant women.<sup>12</sup> The hyphae of the fungi tend to grow well into the epithelial layers making it difficult to remove the thrush patches by simple cleansing. Moreover, the yeast cells and spores are not easily destroyed by antiseptics.

Treatment consists in the removal of all thrush patches by gently but thoroughly swabbing the vagina with a 5 per cent solution of sodium bicarbonate or a diluted solution of green soap. The entire lower genital tract is then gently dried with cotton balls or a stream of warm air. The entire mucous membrane, introitus and labia are then painted with an antiseptic solution. There is no question but that gentian violet, 1 or 2 per cent aqueous solution, affords the most relief from the itching and in controlling the infection. However, the disagreeable staining and messiness is a great disadvantage. A considerable advance has resulted from the introduction of a vaginal cream which combines a low concentration of gentian violet with quaternary ammonium salts and possesses no staining properties whatsoever. The

## RECENT ADVANCES IN OTOLARYNGOLOGY

GEORGE M COATES, MD, FACS,\* AND M VALENTINE MILLER,  
MD, FACS†

### THE EAR

THE literature of the past year contains much material of interest from military sources, particularly regarding atmospheric pressure changes and their effect upon the auditory mechanism and the nasal accessory sinuses. The mechanics of involvement of the two are similar. Many of the articles review what we already know, but repetition is important in fixing important points in our minds.

**Ear Problems in Aviators**—Chester and Drooker<sup>1</sup> state that aerosinusitis is not frequent among Army aviators but that ear symptoms are common. In ascent the positive pressure within the middle ear is increased as the atmospheric pressure decreases and, if the eustachian tube is freely patent, the air in the middle ear readily escapes and there is no lasting effect. If, however, the tube is blocked, a feeling of fullness develops in the ear, with deafness and tinnitus, followed by pain and vertigo if the pressure is not relieved. On descent the dangers to the hearing mechanism are greater, as the increasing atmospheric pressure causes a negative pressure in the middle ear. During ascent the eustachian tubes automatically open to relieve the positive pressure in the middle ear, but during descent entrance of air requires voluntary opening of the tubes, due to their "flutter valve" action. Severe pain develops in the ear if the negative pressure reaches 16 mm, and the tympanic membrane ruptures if 100 mm or more of negative pressure develops. If negative pressure is maintained in the middle ear for any length of time, definite pathologic changes take place in the tympanic membrane and the middle ear. Treatment consists of shrinkage of the mucosa about the eustachian orifice and gentle inflation of the ear. Wiseheart<sup>2</sup> advises the use of the Proetz displacement method with ephedrine 0.5 per cent, or tuamine 0.25 per cent in normal saline. Following this the patient is given a vasoconstrictor, usually a benzedrine or a tuamine inhaler, to use at intervals. Best results were gained when this treatment was started within thirty minutes after the onset of symptoms. The same type of middle ear involvement occurs in divers, submarine personnel and workers in caissons, and Thorne,<sup>3</sup> working with such men at the Norfolk Navy Yard, treated them by

\* Professor of Otorhinology, Graduate School of Medicine, University of Pennsylvania, Emeritus Professor, School of Medicine, University of Pennsylvania.

† Assistant Professor of Otolaryngology, School of Medicine and of Otolaryngology, Graduate School of Medicine, University of Pennsylvania.

drying powder such as that described for *Trichomonas vaginitis*, or frequent daily application of neoarsphenamine, 10 per cent in glycerin, or frequent applications of gentian violet. We have found the use of sulfonamide jellies or creams to be highly effective in the treatment of this condition and much more convenient than the previous methods. For this purpose we have used particularly a cream containing three sulfonamides\* each of which becomes effective at different pH levels. Five cubic centimeters of the cream are introduced twice daily into the vagina and removed after eight hours by a simple cleansing douche.

Recent studies indicate that jellies containing penicillin are also effective in the treatment of this condition, as is penicillin given parenterally.<sup>14</sup>

#### VULVOVAGINITIS IN CHILDREN

Vulvovaginitis in children is generally classified as "specific" when it is caused by the gonococcus or "nonspecific" when due to other causes. The nonspecific type of vaginitis in children may result from the introduction of foreign bodies into the vagina, local irritation from manipulation or tight clothing, uncleanliness or low grade infections with a variety of organisms. Because of the delicate nature of the epithelial lining of the vagina together with its neutral or alkaline secretion, this structure in little girls is especially susceptible to bacterial infection.

In the treatment of *gonococcal vulvovaginitis* the first essential is strict isolation in order to prevent contamination of the other children in the household or institution. Care should be taken to prevent infection of the eyes or spread of the infection to the rectum. The local use of antiseptics and douches which formerly required many months and sometimes years of persistent therapy to effect a cure have now been replaced by treatment with estrogenic hormone, sulfonamides or penicillin. Each of these methods possess certain advantages and disadvantages.

Estrogenic therapy may be given to cooperative children in the form of vaginal suppositories. A suppository containing 0.05 to 0.1 mg. of stilbestrol is inserted each night into the vagina. This is continued for three weeks after which smears are taken at weekly intervals until three negative smears have been obtained. If a cure cannot be effected with two courses of estrogenic therapy it is usually better to proceed with either sulfonamides or penicillin in order to avoid inducing premature sexual changes.

In children in whom local treatment is not possible or feasible, stilbestrol may be given orally 0.1 mg. daily for two to three weeks. If

\* Triple-Sulfa Cream, generously supplied to us for clinical investigation by Ortho Pharmaceutical Corp., Linden, New Jersey, contains micronized "sulfa" drugs (identified as sulfathiazole, acetylsulfonamide and benzylsulfanilamide) in a suitable base, nonbuffered to permit optimal pH effectiveness for the "sulfa" compounds.

bone Persons within a radius of 50 feet of a 200-pound bomb explosion, who are not protected by a raid shelter, probably will have ruptured drums with bleeding from the ears At a greater distance hemorrhage into the ear drum may occur Wilson<sup>9</sup> made a study of the effect of the "basic" course of firing on the hearing of eighty-five army inductees The results indicated that persons with some impairment of hearing are more susceptible to acoustic trauma than those with normal hearing, that some persons are more susceptible to acoustic trauma than others, and that ears so predisposed are fatigued more readily The "fatigue test" seems to be a means of determining the individuals who are apt to sustain traumatic deafness This consists of exposing the right and then the left ear to a 256 cycle fatiguing tone at 80 decibels intensity for five to eight minutes Each ear is tested before the test and again one minute after it In industries where acoustic trauma occurs, this test might be a means of "screening out" susceptible persons Palmer<sup>10</sup> reported some rather surprising figures from a group of Indian troops injured by the explosion of a land mine Of eighty-two survivors of the explosion, all of whom were within a radius of 15 yards of it, sixty had perforated drum membranes (100 perforations in all) All showed conduction deafness by tuning fork test The majority showed diminution of absolute bone conduction for several days after the explosion Sulfanilamide powder was blown into the ears but about 38 per cent became infected, only four of them severely Forty-five per cent healed within four weeks Permanent damage to hearing was slight

Silcox and Schenck<sup>8</sup> made a very interesting report of the ear lesions encountered among the casualties aboard a hospital ship The most common type was traumatic rupture of the ear drum, with or without secondary infection Other forms of ear involvement were traumatic deafness, which was present in varying degrees in almost all, hemorrhage into the middle ear, dislocation of the ossicles and hemorrhage into the labyrinth The causes of the damage were (1) atmospheric blast from explosions and (2) immersion blast from explosion of depth charges when the patient was in the water Factors in the development of aural damage are (1) the proximity of the source of the sound or the center of detonation, (2) the character of the concussion waves, whether atmospheric or immersion blast, (3) the duration of exposure to the sound stimulus, (4) the awareness of the subject that a blast is impending, (5) the presence or absence of previous aural disease and (6) the use of protective devices Blast waves from high explosives have a marked effect upon the hearing of a person within the "critical distance" of the center of detonation, which has been estimated to be about 20 feet (6 meters) in air, and approximately four times that distance in water Atmospheric blast waves have two phases, first, a compression phase lasting approximately 0.005 seconds, and second, a suction phase lasting about twice that long The pressure exerted by the first phase varies inversely with the square of the distance and reaches its maximum intensity in 1 millisecond The magnitude of both components is directly proportional to the size of the charge used, and the resulting damage depends upon the intensity and proximity of the sound

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sac Lindsay<sup>12</sup> recently reported another case of histologic examination which also showed dilatation of the endolymphatic spaces

Atkinson<sup>13, 14</sup> divides cases of the syndrome into allergic and vagospastic by the histamine sensitivity test. The former are treated with *histamine* and the latter with *nicotinic acid*. In allergic cases he gives histamine base in gradually increasing doses, never over 0.57 mg, until tolerance is determined. Of fourteen cases twelve were definitely relieved, one improved and one relapsed. In nonallergic cases he believes the vertigo to be due to primary vasoconstriction and gives nicotinic acid for its vasodilator effect, beginning with 25 mg by intramuscular injection and gradually increasing the dosage. The average maximum dose is 50 mg by injection and 50 to 100 mg by mouth. The drug is given at the maximum for one month and then gradually decreased, but continued for many months. Of forty-nine patients, twenty were entirely relieved, twenty-five improved and four no better.

Cawthorne and Hallpike<sup>15</sup> feel that histamine has been of use in about one third of their cases. They also employ a combination of  $\frac{1}{800}$  grain of hyoscine and  $\frac{1}{150}$  grain of hyoscyamine in tablet form, 1 to 3 tablets being taken daily. If this caused a blurring of the vision or a dryness of the throat with dosage sufficient to control the attacks, dosage may be reduced, or a mixture of  $\frac{1}{2}$  grain of luminal and  $\frac{1}{12}$  grain of pilocarpine may be given two or three times a day. If the attacks cannot be controlled by conservative measures, these authors abolish the function of the labyrinth by opening the horizontal canal and destroying the membranous canal within it.

In view of the vasomotor disturbances which are common to migraine and Ménière's syndrome, Schick<sup>16</sup> has treated the latter by the method which he found brought good results in migraine. This consists of intravenous administration of a 50 per cent solution of *magnesium sulfate*, the injection is given very slowly with the patient lying down, and the patient experiences no discomfort. An injection of 5 cc was given two or three times a week, and from ten to twenty injections were given depending upon the severity of the symptoms and the response to the treatment. Of eighteen patients, seven have been free from symptoms for fourteen months and seven greatly improved, with a reduction in the number and severity of the attacks, no vertigo between attacks, and with tinnitus and hearing improved. Four showed no improvement.

**Deafness and Hearing Tests**—Kobrak<sup>17</sup> reported some interesting animal experiments in the *transmission of sound* through the ossicular chain and the nonossicular (aerocochlear) route. With sounds at the threshold level, aerocochlear conduction could not be demonstrated, but with higher intensities aerocochlear conduction was found to play a definite role. From previous study it has been found that the elastic qualities of the ossicular chain are modified by contractions of the intratympanic muscles. Tones of low intensity do not cause such mus-

whitish plaques on a red base which may be secondarily infected due to the patient's scratching. At times the secondary infection may be so pronounced that the condition may resemble follicular vulvitis. Diagnosis is made on the characteristic appearance of the lesion, finding sugar in the urine, and positive smears for the fungus. Culture may be necessary to identify the organism in unusual cases.

Treatment is aimed at eliminating the glycosuria plus the local application of 2 to 5 per cent aqueous solution of gentian violet repeated as often as at twenty-four hour intervals. This latter gives prompt and complete relief from the pruritus which is usually the patient's complaint. It is important to remember that the entire vulva and vagina must be treated with the gentian violet solution when it is applied, otherwise the condition will persist.

**Condylomata Acuminata.**—These papillomatous lesions of the vulva, often improperly diagnosed "venereal warts," are not venereal in origin but are due to a virus. They may be found in association with venereal disease, and are to be differentiated from condylomata lata which are syphilitic in origin. Lesions may be few or many in number, vary in size from pin-point to several millimeters in diameter and height, and occur in crops on the vulva and in the vagina. They are sometimes seen in pregnancy and, if left alone, frequently disappear after the gestation has terminated, without treatment. When removal is necessary because of bleeding and irritation (they rarely undergo malignant change) excision using the electrocautery is probably to be preferred. Local applications are of no value.

**Pruritus Vulvae.**—Itching of the vulva is one of the complaints often encountered in gynecologic practice. Sometimes its cause may be obvious; more frequently investigation will reveal its background; quite commonly no cause can be determined and we are wont to ascribe the complaint to some form of psychoneurosis. In this latter attitude we may be wrong; it is possible that we have not studied the patient sufficiently or observed her for a satisfactory period of time to make the correct diagnosis. The more common causes of itching involve the specialties of medicine, dermatology, urology, proctology, and gynecology. Accordingly the stubborn case should be studied from these angles. Diabetes, jaundice, rectal conditions and parasites, diseases of the urethra and periurethral glands, infections of the genital tract, atrophic and degenerative changes in the vulvar skin due to estrogen deficiency (?), the various dermatologic lesions which cause itching in other parts of the body, local allergy to vulvar pads, talcum powder and the like, and last but not least, poor hygiene—any can be a cause of itching of the vulvar skin. Thus investigation should include urinalysis, smears, examination of any discharge by the hanging-drop method to exclude trichomoniasis, rectal examination, pelvic examination, and a careful examination of the status of the affected skin itself. Moreover, the serologic examination should not be neglected.

as indicated. In all cases natural vitamin B complex concentrate made from rice bran is given, together with 10,000 units of vitamin A in combination with vitamin D. All patients are required to drink orange or grapefruit juice and the juice of half a lemon daily. At least two glasses of whole or skimmed milk or buttermilk should be given, and some form of cheese and a raw vegetable salad made up of at least six vegetables are to be taken at noon. Office treatment is given semi-weekly for about two months. Intramuscular injections of 8000 to 16,000 units of thiamine hydrochloride, and 5 to 10 units of plain insulin are given first. Before the injection each ear is exposed to infra-red heat for five minutes. Next 95 per cent alcohol, followed by boric acid ointment, is applied to the external canal. Following a series of thiamine injections, niacin is used in doses of from 25 to 50 mg, with 5 to 10 units of insulin. Finally  $7\frac{1}{2}$  to 15 units of liver concentrate are given. After the injections are completed the patient continues with the diet, plus supplementary oral vitamin therapy. At intervals hearing tests are made and, if necessary, an additional series of injections is given. Among the outstanding general improvements noted are decreased fatigability, cure of constipation, increased appetite, increased strength of the nails, clearer skin and improved cerebration. The rationale of the thiamine, niacin, insulin, and liver therapy is given by the author.

Gilding<sup>23</sup> makes a preliminary report on *audiometric and word test findings*. The initial study of patients included the pure tone audiometer test by air and bone, and the Rinne, and Weber tests, and for speech, by phonograph attachment to the audiometer and by the unamplified voice. Subsequent tests included only pure tone audiometer and phonograph word tests, in both of which the intensity was controlled. The study indicated a correlation between hearing for pure tones and hearing for words. If the audiogram shows a decibels loss greater than 20 at any frequency, the word test invariably falls below 90 per cent. It was found that loss of the lower tones affects the hearing for "fundamental voice tones." Loss of middle tones affects chiefly the hearing for vowels and some consonants, and loss of high tones affects hearing for consonants. Gilding speaks of a type of high tone deafness which she calls "developmental high tone deafness" in which the hearing is approximately normal for the low range. These people have normal hearing for voice sounds and some of the vowels, but impaired hearing for soft-toned consonants. They may pass numbers tests with a perfect score but cannot pass the word test. Speech development in these persons is delayed but eventually is normal.

The incidence and permanence of *tonal dips* was studied by Loch<sup>24</sup> in 1365 school children aged from eight to fourteen years. A dip of at least 15 decibels at any point below the average for the audiogram was considered a "tonal dip." For tones below 512 double vibrations and above 4096 double vibrations the depression must be 20 decibels or more. Dips were found in 15 per cent of boys and 5 per cent of girls. Older children show greater frequency of dips than younger children. About one half of all dips occur at 4096. It has been noted before that tonal dips are more frequent in men than women, and this

present, may cause dermatitis in unskilled or even skilled hands. Ultimately, in patients with dyspareunia and pruritus, the treatment of choice is vulvectomy. Asymptomatic atrophic changes may be treated with conservatism; as a matter of fact they require no treatment.

**Leukoplakic Vulvitis.**—Better called *leukoplakia of the vulva* because leukoplakia may be observed on any epithelial surface, leukoplakic vulvitis is a local or diffuse whitish thickening of the skin of the vulva and perianal areas, with or without the formation of fissures. The condition often seems to develop in the perineal and perianal areas, spreading forward to include the labia and clitoris and backward to involve the gluteal cleft. Pruritus is the chief complaint again, but the condition may be entirely asymptomatic. Secondary infection may be present following scratching. The cause of this condition is not known.

Treatment by hormones (estrogens and androgens) as advocated by some clinicians has not been generally accepted because the late Doctor Taussig, in his monumental work on this condition, showed that over 50 per cent of the patients he treated for carcinoma of the vulva suffered from leukoplakia of the vulva before the carcinoma developed. Accordingly, the condition has become recognized as a definite pre-cancerous lesion and the treatment of choice, either in symptomatic or asymptomatic cases, is vulvectomy.

#### ULCERATIVE AND HYPERTROPHIC DISEASES OF THE VULVA

Hypertrophic ulcerations of the vulva, some of which are associated with the development of fistulas, require careful study for their diagnosis and differentiation one from another. Included under this heading are chancroid, lymphopathia venereum, granuloma inguinale, tuberculosis, syphilis, fusospirochetosis and carcinoma. A definite routine of study is necessary when any such lesion of the vulva is encountered.

**Chancroid.**—Chancroid, a venereal disease seen more often in men, is associated with a lack of cleanliness. The local lesion consists of a painful pustule which ulcerates superficially leaving a reddish granular base without surrounding induration and extremely painful to touch. The lesions may be multiple due to autoinoculation. Inguinal bubo develops early and is often unilateral when present. It may slough or rupture spontaneously and drain freely for some time. The infection does not become systemic. The causative organism is the streptobacillus of Ducrey which can be identified by smear and culture. The intradermal injection of killed organisms produces a local reaction (Ducrey test) which is diagnostic.

Treatment consists of the use of sulfanilamide both locally and systemically. Allantoin cream or jelly applied locally favors healing of the ulcerations. Buboec when present are preferably treated early, before rupture, by aspiration. Penicillin has not yet been used sufficiently to permit an estimate of its value in treatment.

is caused by autonomic system involvement, or is associated with the cardiovascular system in older patients, the patient is given two or three tablets of glycerol trinitrate ( $\frac{1}{100}$  grain) and told to take one when he feels an attack coming on, or when the tinnitus recurs or increases in volume. Attacks of tinnitus and accompanying deafness can often be aborted and this results in decreasing the frequency and the severity of the attacks.

### NOSE AND THROAT

**Common Cold.**—The common cold is receiving more attention than in the past and several new methods of prophylaxis and treatment have been suggested. Harris and Stokes<sup>28</sup> used *glycol vapors* in bactericidal concentrations in three wards of a children's convalescent home, using three other wards as control. Patients were, with few exceptions, confined to bed, so there was infrequent direct contact. There were only three cases of colds in the vaporized wards compared to seventy-nine in the control, and the results indicate, the authors believe, that glycol vapors are viricidal as well as bactericidal. The experiment seems also to give some evidence of the airborne transmission of the common cold.

From Britain come reports of the therapeutic effects of *patulin*, which is a derivative of *Penicillium patulum*. Gye<sup>29</sup> tried it on himself and several others, mostly physicians, and only one did not respond. It was used as a nasal douche in 1:20,000 solution buffered with phosphate at a pH of 6.0. Hopkins<sup>30</sup> reports that the drug is about as effective against gram-positive as against gram-negative organisms, it is less effective than penicillin against gram-positive organisms, but much more effective against gram-negative organisms. The presence of serum or pus does not affect its bacteriostatic power. The phagocytic action of leukocytes in vitro was not affected by a 1:8000 solution, but was inhibited by a 1:2000 solution. Patulin was used in the treatment of Navy personnel. Three groups were treated with patulin, each with a control group. Phosphate buffer solutions (pH 6) of 1:20,000, 1:10,000 and 1:5000 were applied locally in the nose and nasopharynx or snuffed up out of the hand, and in some cases used as a gargle. In the patulin treated cases 57 per cent recovered completely within forty-eight hours, in the control group only 9.4 per cent recovered in forty-eight hours. Greenwood<sup>31</sup> further analyzes the results and shows that where the symptoms of the cold had been present for less than one week, 54.7 per cent recovered within forty-eight hours under patulin, while only 9 per cent of the untreated group recovered in that time. There were twenty cases with symptoms present more than one week and 70 per cent of these recovered promptly under patulin, while in the control group treated by other methods 13.6 per cent recovered promptly.

**Sinus Infections.**—A new sulfa compound, *desoxyephedronium sulfathiazole*, or "D.O.E. Sulfa," has been reported by Turnbull, Hamil-

tion with the tubercle bacillus. Infection may take place through a break in the skin or through the blood or lymph stream. The lesion is usually a chronically ulcerating growth with elevated edges and an irregular grayish-red granular base with some surrounding infiltration. The ulcers may be superficial or deep, even causing fistulous tracts connecting with the bowel, bladder, or the urethra. The diagnosis is made by making smears and taking a biopsy after suspecting the presence of the condition. The microscopic picture is necessary for certain diagnosis, but even here, granulomas of the vulva due to foreign bodies such as talcum powder may give a microscopic picture which can prove confusing even to the experienced observer.

Treatment will vary with the nature and extent of the lesion; if it is purely local, excision is preferable; if it is too extensive for complete excision, then x-ray treatments are preferable to the application of radium locally because of the sloughing effect of the latter. In the presence of general infection local treatment is without effect except as a palliative.

**Syphilis.**—In the vulva, syphilis may appear as either the primary, secondary or tertiary lesion. The primary lesion or chancre may be anywhere but is usually on the labia, vestibule or fourchette. It is a small, elevated, firm, nontender ulceration with a grayish base which exudes serum when the slough is removed. It may be single or multiple due to autoinoculation where folds of vulvar skin are in apposition. Diagnosis is made by darkfield examination which may have to be repeated. The secondary lesions may appear as condylomata lata or mucous patches. Darkfield examination is used here for diagnosis but in the event it is negative, biopsy should be made. The serology is usually positive by the time the secondary lesions manifest themselves. The tertiary lesion or gumma is unusual and for diagnosis biopsy of the edge and surrounding tissue is necessary together with serologic examination. Treatment is standard.

**Fusospirochetosis of the Vulva.**—Fusospirochetosis or Vincent's infection of the vulva is occasionally seen. Whether this is a primary or secondary infection is not usually clear. The vulvar skin is edematous and macerated with few or many sloughing, acutely tender ulcerations which are associated with a fetid, acetic discharge. Smears from the ulcerations show the fusiform bacillus and the spirillum. The source of the infection is not always clear, but the use of saliva from an infected mouth as a lubricant during coitus has been considered as a possible mechanism.

Treatment is both local and general. Bed rest is desirable because of the systemic reaction which is often present and the severe pain. Sodium perborate or potassium permanganate douches help local hygiene. Arsphenamine or mapharsen locally and intravenously help to bring relief more quickly. Penicillin is reported to be very effective locally in oral infections and should help greatly here.

before the period (premenstrual hypo-ovarianism) Occasionally there is a more or less spastic nasal syndrome Nasal congestion, hemorrhage and sneezing may occur during menstruation Hydrorhinorrhea may simulate spastic rhinitis Sphenopalatine syndromes may be due to endocrine disturbances

Rhinopathies have been seen in women with an overproduction of estrogens, and in the initial stage of the menopause the increased output of estrogen may cause nasal symptoms In pregnancy *spastic nasal syndromes* improve with the decrease in estrogens In pregnancy, too, the corpus luteum hormone exerts a protective action in the hyperexcitability of the neurovegetative system The authors suggest that, as estrogen favors mobilization of glycogen, there may be some hepaticogenital relation in the pathogenesis of spastic rhinitis of endocrine origin Abnormal estrogen hyperfunction causes hypocalcemia, diminution of acids in the blood, with resulting hyperexcitability of the sphenopalatine ganglion and vasomotor nerves of the nasal mucosa In any of the genital periods there may be marked vasodilation of the pituitary mucosa capable of causing more or less severe *epistaxis*, due to the vasodilating action of the sex hormones on the central circulation and the cephalic mucosa The epistaxis of genital origin coexists with menstruation and menorrhagia, but is not vicarious All degrees of change in the sense of smell may be seen in gonad-symphathoses, owing to the obstruction of the olfactory fissure In some cases there is a lack of secretion in the nose and gonadal deficiencies may cause an increased susceptibility to nasal infection

Possibly<sup>37</sup> some connection exists between *hypertrophy of the pharyngeal tonsils* and vegetative imbalance with predominance of the vagus due to endocrine dysfunction Tonsillar and pharyngeal manifestations of gonad origin are seen chiefly in women during sexual periods The thymicolymphatic system begins to undergo involution when the testes and ovaries attain their full hormone activity If the gonad development is arrested, the thymicolymphatic system persists The development of Waldeyer's ring is usually slight in sympathicotomies, although in eunuchs the pharyngeal lymphoid tissue is markedly developed Adenoidism is common in Fröhlich's syndrome, and in cases of neurovegetative hyperirritability one finds hypogonadism and hypoadrenalism with hypertrophic thymus function and hypertrophy of the lymphatic ring The authors describe a genital effect on the pharyngeal mucosa, suggesting a genital origin for chlorosis, and call attention to the senile involution of the mucosa with the decline of genital function Cyclic changes have been observed including dysphagia, odontalgia and other disturbances of oral and pharyngeal sensibility There may be edema of the uvula and lingual surface of the epiglottis Severe edema of the uvula and tonsils in pregnancy may disappear following delivery, and many cases of uvular apoplexy occur during menstrual periods Gonadal effects upon the pharynx run a regular course, the objective symptoms lasting for four to ten days and then subsiding until the next period, but poor circulation may persist in the mucosa after the period Patients may suffer from spasmodic contraction of the pharyngeal constrictors and there may be atrophy of the pharyngeal

**Carcinoma of the Vulva.**—Vulvar carcinoma is the third most frequent form of genital cancer in the female, being preceded only by the uterine and ovarian forms of malignancy. It may be primary or secondary, the former being by far the most common. It is a disease of advanced age since most reported cases have occurred in the seventh decade of life. The more common sites of origin are the labia, clitoris, vestibule and urinary meatus, and rarely Bartholin's gland. Histologically the growth may be epidermoid or adenocarcinoma depending on the site of origin, the former being more usual. The condition begins as a small nodule, asymptomatic at first, which gradually increases in size and eventually ulcerates. This is what usually brings the patient to the doctor. The diagnosis, when suspected, is confirmed by biopsy. Carcinoma of the vulva, except the clitoris, develops slowly.

Most cases occur in the anterior portion of the vulva from which the lymphatic drainage is through the inguinal nodes. When recognized early, carcinoma of the vulva can be cured by radical vulvectomy and excision of the superficial and deep inguinal glands (Bassett's operation) as advocated by Taussig who claims above 50 per cent cures. Secondary carcinoma, although rare, may be seen and represents metastasis from other genital cancers or chorioepithelioma. The treatment is palliative.

#### THE PROBLEM OF SEXUAL DISSATISFACTION

The role played by the physician in the management of the problem of sexual dissatisfaction, and the related problems of dyspareunia and vaginismus, is that of confessor and adviser. Usually the patient is distraught with fears—fear of the permanency of her marriage, fear that she is not a good wife, and so forth and finally consults a physician in desperation. She does not blurt out her story in so many words; usually it is a long-drawn-out recital of vague pelvic complaints for which the physician can find no basis in actual pelvic disease. Then when he explains that he can find no pathologic changes, and solicitously inquires just what did cause her to come to his office, the true story slowly emerges. Haste is dangerous at this point; it must be remembered that from the patient's viewpoint she is making a confession. The story unfolds slowly because often in the patient's mind it is a confession of her sexual inadequacy. Most often we know that this is a complex built up as the result of a thoughtless or unadaptable husband who is more concerned with himself than their mutual well-being. Here the physician is confronted with a problem which he can solve by using a combination of sympathetic understanding and judicious questioning. The patient cannot be hurried—adequate time must be allowed for her to collect her thoughts and express in her own way the background of her troubles. If for any reason the physician is unable to give such a patient sufficient time, he had better refer her



too, that the recurrence of nasopharyngeal lymphoid tissue after adenoidectomy, if done before puberty, is so common that it must be considered a normal reaction. The author has treated 250 patients with nasopharyngeal lymphoid masses by means of radium, using an applicator containing 50 mg of radium in a platinum capsule. This is attached to a copper wire 7 inches long, and both are covered with gum rubber 0.7 mm thick. After anesthesia of the nasal mucosa, this applicator is passed through the inferior meatus and each side is given a 2 gm.-minute treatment. Postnasal discharge cleared up in 234 of the 250 cases. Eleven allergic patients failed to respond, although five of these did so following a second treatment. No excessive dryness resulted. Hearing was improved in thirty-seven bilateral conduction deafness cases. In four patients with perforated drums the discharge stopped.

Because it was realized that sufficient study of the *indications for the removal of tonsils and adenoids* had not been made in children referred for operation, a Pretonsillectomy Clinic was established in New York's Mt. Sinai Hospital.<sup>41</sup> In determining the indications, a careful history is necessary, especially in regard to upper respiratory infections and the possibility of allergic conditions. Tonsillectomy is advised in the following conditions: defective hearing or chronically inflamed ear drums, mechanical interference with respiration (in some of these cases the authors believed adenoidectomy alone was indicated, in others operation was deferred if the child was under three or four years of age), large and diseased tonsils associated with frequent upper respiratory infection and recurrent glandular involvement, and rheumatic disease.

Berberich<sup>42</sup> believes that bismuth will cure *tonsillitis* more rapidly than any other treatment. He gives sobisminol mass in capsules, each capsule representing 150 mg of elementary bismuth. For adults, 4 to 6 capsules are given the first day, 3 to 4 the second. For children 3 to 4 are given the first day and 3 on the second. The capsules are equally effective by mouth and rectum. In the latter use both ends of the capsule are punctured before insertion. If an acute tonsillitis is not relieved after forty-eight hours, some other condition, such as diphtheria or peritonsillar abscess, should be suspected. The capsules are effective in Vincent's infection, 2 capsules being given three times a day the first day and twice a day the second. They are helpful in pharyngitis granulosa with exudate, but not in other types of pharyngitis.

Based upon finding lesions in pellagra similar to those of *Vincent's infection*, King<sup>43</sup> in 1940 reported the use of nicotinic acid in the latter infection. Johnson<sup>44</sup> reports following this up and treating patients with niacin, 25 to 50 mg three times a day for adults, and 10 mg or more for children according to age. The results were satisfactory and "most spectacular" in acute cases.

that selfishness combined with a lack of consideration and frequently a total ignorance of the elements of coitus on the part of the husband is a far more common cause of sexual dissatisfaction than any supposed or imaginary sexual inadequacy on the part of the wife. There are no more grateful patients than those for whom a problem of this type has been solved by the physician.

The essentials of success in the management of these problems are first of all a sympathetic understanding by the physician of the true situation which exists, tactful questioning of both husband and wife after each has told his or her story to the physician; a careful explanation of the purposes of sexual relations; a brief explanation of the male and female anatomy to both parties, and finally a note of caution to the husband that the old proverb "haste makes waste" applies even to such things as sexual relations.

this regulates the pitch (The shorter the column the higher the pitch) Secondly, these gross movements of the larynx have a distinct influence on the tension of the vocal cords. The cords may be shortened both actively and passively, but can be lengthened only passively.

### ALLERGY

Failure to treat *allergy in children* adequately often leads to complications and secondary changes which make treatment more difficult, such as nasal polyps, secondary infections, development of nasal and facial deformities (Crip<sup>48</sup>). In children from birth to fourteen years (Miller<sup>49</sup>) allergic reactions most frequently involve the respiratory tract, either as allergic rhinitis or bronchial asthma, or both. Skin tests may not be successfully used in children under six, but passive transfer tests may be made, using the father if possible. The most frequent allergies in children under fourteen are found to be caused by bacteria, feathers and dust, wheat, chocolate, eggs and milk. All supportive measures must be used, including vitamins in large doses.

Davidson<sup>50</sup> made a study of the allergic activity in *house dust*. He used one hundred patients, all of whom reacted to all of the house dusts used. Eight stock house extracts and thirteen "autogenous" extracts were used, and each patient was tested with from one to five extracts. The reactions were compared with reactions to common ingredients of house dust. It was found that horse dander was the most active, giving positive reactions in thirty-two. Cat hair gave positive reactions in sixteen, and cow hair in fourteen. Feathers gave fewer reactions than was expected, but this may have been due to a lower potency of the extracts. The author's examination of house dust indicates that it contains cotton, flax, jute, wool, silk, six or more animal hairs, three or more feathers, glue, kapok, orris root, pyrethrum and tobacco.

The idea that the presence of allergy predisposes to infection seems disproved by the work of Frank, Blahd and Howell<sup>51</sup>, whose experiments show no difference in the susceptibility of the normal individual and the allergic to pathogenic organisms.

*Histamine* as a therapeutic agent in allergy is being used increasingly, and Gurling<sup>52</sup> treated 120 cases with it after giving intradermal tests with 0.01 cc. of a 1:100,000 solution of histamine disphosphate. An area the size of a quarter dollar was considered positive. In treating positive reactors dilutions of 1:100,000 to 1:1,000 were used, and treatment was carried out in such a way as to avoid reactions. If a reaction occurred, the next dose was reduced to two thirds the last dose. The number of doses required was 25 to 40. After the course was completed the intradermal reaction was greatly reduced or absent. Of seventy-three patients, seventy were completely relieved of nasal allergy, of fourteen cases of nasal allergy and conductive deafness, five were relieved and eight partially relieved, twenty cases of "lower half headache" with nasal symptoms showed fifteen entirely relieved, five

proliferation and differentiation of the granulosa cells and ingrowth of the theca lutein cells.

*The Progesterin Phase.*—In a dual capacity the corpus luteum continues the elaboration of estrogenic principle and also produces another hormone, termed progesterin. This transforms the estrogen primed endometrium into a premenstrual state suitable, should an ovum become fertilized, for nidation.

In this phase the mucosa becomes differentiated into three distinctive layers: (1) a compact surface layer, (2) an intervening spongy layer, and (3) immediately overlying the myometrium a basal layer. Marked secretory activity of the surface cells, but more particularly those of the glands, is evident. The epithelium lining the glands is composed of large cells with basal nuclei.

The stroma also shows specific changes. A thin layer of lightly stained large polygonal stroma cells with large round nuclei forms the compact layer of the mucosa. These cells, however, are not equally developed in all areas. They are not unlike the decidual cells of early gestation and are termed pseudodecidual cells. In the middle or spongy layer are found characteristic markedly tortuous glands, closely packed, but separated from each other by strips of stroma cells. The gland lumen is filled with secretion. The basal layer is unchanged. The histology of the progesterin endometrium is similar to that of a two weeks' gestation and only the absence of chorionic villi distinguishes it.

The true premenstrual stage is the period from the cessation of actual production of progesterin to the onset of bleeding and is only about forty-eight hours in duration. The coiled endometrial arteries constrict at the base with a peripheral ischemia and the stroma of the endometrium becomes dehydrated. Subepithelial hematomas appear coalescing into lacunae which begin to bleed into the lumen.

*Types.*—There are, according to the modern concept of menstruation, two different types of a menstruating mucosa:

1. *Normal.*—In this type, the functional layers (compacta and spongiosa) are dismantled, leaving a raw wound, the base of which is formed by the altered basilar layer. This is the most common type.

2. *Pseudomenstruation.*—In this form, menstruation occurs from an inactive or almost resting mucosa. There is no evidence of the premenstrual phase in the mucosa, uterine bleeding occurring from an estrogenic endometrium. This periodic bleeding is not a genuine menstruation, because it is not associated with the characteristic preparatory endometrial changes nor with extensive endometrial desquamation. This inadequate preparation of the endometrium makes proper implantation of the fertilized ovum impossible and explains many cases of sterility in regularly menstruating women.

Other possible causes of pseudomenstruation besides failure of ovulation are imbalance of the two ovarian hormones, estrogen and progesterin, and a uterus which fails to respond to normal ovarian stimulation.

In studying cases of menstrual disorders, a diagnostic premenstrual uterine curettage is important in that it shows the end result of the effect of both estrogen and progesterone activity on the endometrium. If the endometrium is normally responsive the type of ovarian dysfunction can be determined. Day-to-day vaginal smears also determine estrogenic effect and cyclic ovarian changes. The probable date of

trophv and sneezing were also relieved In selecting cases for injection, the ability of the turbinates to shrink was determined. One-half per cent pontocaine is used for anesthesia and the sylnasol solution is injected with a 2-inch needle, 23 gauge, on a 2 cc tuberculin syringe The needle is inserted the entire length of the turbinate, care being taken not to make a counter puncture As the needle is withdrawn a full 0.5 cc is slowly injected Some retrobulbar discomfort may be felt for five to ten minutes at most Occasionally there is transient dental pain If any of the agent drops into the throat there may be an acrid taste and a burning sensation with some cough for a few minutes After that only nasal obstruction remains Nasal sprays may be used only if the patient is very uncomfortable In from three to five days the reaction begins to subside and in from seven to ten days actual shrinking can be seen This continues for five to seven weeks There is a marked reduction in nasal mucus so that postnasal drip is relieved

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advanced pulmonary tuberculosis. The primary anemias are generally associated with the condition, as may be diabetes, chronic nephritis, and tuberculous infections other than those involving the lungs. It may result from profound nervous shock, and it occurs in the advanced stages of organic nervous disease. In Manila it was recently reported that in many patients the menses stopped abruptly after the first bombing or soon after internment and before a food deficiency could have any effect.

2. Acute Infectious Diseases.—Amenorrhea is often present during convalescence from the acute exanthemas, typhoid fever, malaria and influenza.

3. Climatic Influence.—Exposure to wet and cold, with sudden chilling of the body or a simple change of environment may result in a temporary check of the menstrual process.

*Local Causes.*—1. Primary.—The most common local cause of amenorrhea is congenital ill-development of the organs fundamentally concerned in menstruation. Usually the uterus and ovaries are involved, the hypoplastic alteration in the uterus being secondary to that in the ovaries. Hypoplasia of the latter organs may not be congenital, but may represent some pathologic alteration which had its inception in early adolescence. Irregular development of the genital organs, especially an imperforate hymen or stenosis of the vagina or cervix, results in a failure of the menstrual flow to appear.

2. Secondary.—Radical curettage or prolonged radium treatment may cause amenorrhea by destroying the endometrium.

Follicle cysts of the ovary as a cause of amenorrhea are not infrequent. These may result from the inability of the ovum to penetrate an inflamed, thickened tunica albuginea, or more commonly, may be due to an insufficient hormonal stimulation from the anterior pituitary gland, so that the follicle fails to rupture. If the follicle does not rupture, it becomes either atretic or distended with fluid and forms one or more retention cysts. Occasionally these cysts elaborate a sufficient quantity of estrogenic hormone to produce prolonged menstrual bleeding.

*Endocrinopathic Causes.*—Disorders of the endocrine system may be associated with amenorrhea and this is especially true of the anterior pituitary gland and ovaries. These disturbances may be classified as: 1. Primary Pituitary Deficiency.—Primary deficiency of the anterior pituitary lobe is by far the most common form of endocrine disturbance encountered. Generally speaking, this condition, if not sufficiently severe to suppress totally ovarian function, is usually one of a mild Fröhlich's syndrome (adiposogenital dystrophy). Clinically, these patients are rather short in stature and show distinct stigmas of under-activity of the hypophysis, manifested first by a characteristic mammary mons girdle obesity due to associated involvement of the hypothalamus, secondly by hypertrichosis with masculine distribution

## RECENT ADVANCES IN CARDIOVASCULAR DISEASE

THOMAS M. McMILLAN, M.D., F.A.C.P.\* AND SAMUEL BELLET, M.D.†

It is one of the paradoxes of war that in spite of its tragedy and waste, medical knowledge is nearly always advanced. Although the type of formal research that goes on during peace has largely ceased, nevertheless a broader form of clinical investigation, the opportunity for which exists only during war, is being vigorously carried out.

Because of these circumstances, during the last year the reports in the literature of investigative work are not abundant. Some of these, which have recently been published, will be referred to as the space assigned to us permits. Because of the latter limitation we will omit reference to the peripheral circulation.

### RHEUMATIC FEVER

Although we know little of the details of the studies being made in the Army and Navy, we do know that rheumatic fever is being intensively investigated by very capable workers. We can hope that the observations now being made under the circumstances of war will at least clarify and possibly solve some of the problems of this greatest cause of heart disease in young persons.

One important advance that we wish to refer to does not have to do immediately with clinical research, but is rather in the field of public health in a broad sense. It concerns the fact that the lay public has at last become very much aware of the problem of rheumatic fever, and is ready to do something about it. This can be attributed, first, to the unrelenting efforts of many individual physicians and organizations, such as the American Heart Association and its affiliates, toward the education of the public in this field. It has also undoubtedly been contributed to by the fact that perhaps as many as 5 per cent of those rejected by the Army and Navy in the present war were declined because of rheumatic heart disease, and also because of the fact that rheumatic fever has reached almost epidemic proportions in some Army camps. In the opinion of those who follow these trends the time

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From the Pennsylvania Hospital, the Edward B. Robinette Foundation, University of Pennsylvania, the Division of Cardiology, Philadelphia General Hospital.

\* Associate Professor of Cardiology, University of Pennsylvania, Graduate School of Medicine, Assistant Professor of Clinical Medicine, University of Pennsylvania School of Medicine, Chief, Division of Cardiology, Philadelphia General Hospital.

† Instructor in Medicine, University of Pennsylvania School of Medicine, Associate in Cardiology, University of Pennsylvania Graduate School of Medicine, Assistant Chief, Division of Cardiology, Philadelphia General Hospital.

value in determining pituitary dysfunction in menstrual disorders and whether we are dealing with primary pituitary failure or primary hypogonadism.

2. *Estrogenic Hormones*.—For determination of estrogen in the urine, the urine is first hydrolyzed by boiling for fifteen minutes with 5 per cent hydrochloric acid or sulfuric acid. This releases about 95 per cent of the estrogenic hormone present by converting the inactive to active estrogen. During active sex life, except during pregnancy when there is a huge increase, a woman normally excretes in the urine 150 mouse units of estrogen in twenty-four hours.

There is a rise in estrogen at the time of ovulation followed by a drop and then another rise premenstrually. The highest concentration is noted at the end of the premenstrual stage. A modification of the Allen-Doisy test is usually employed in which the extract is injected into castrated adult mice or rats and varying degrees of vaginal estrus observed.

These are accurate and practical tests to determine the level of ovarian activity. They are of special value in the diagnosis of functional sterility in regularly menstruating women. At the premenstrual phase of the cycle, close to 90 per cent of normal fertile women show a demonstrable quantity of the hormone. In regularly menstruating sterile women, without pelvic disease, a positive reaction is much less frequent, thus indicating a deficiency of estrogenic production.

3. *Progesterone and Its Excretion Product, Pregnandiol*.—Progesterone is metabolized in the liver and excreted in the urine as a water-soluble compound, sodium pregnandiol glycuronate. Pregnandiol has no biologic action but can be determined in the urine by the gravimetric method of Venning and Browne. In menstrual disorders, the presence of pregnandiol in the urine immediately after ovulation in amounts of 3 to 10 mg. is indicative of a normal corpus luteum and ovulation.

4. *Androgens and 17-Ketosteroids*.—A woman normally excretes about three-fourths as much androgen as the male. This is derived from the adrenal cortex. Biologic assay is difficult. Chemical assay for 17-ketosteroids is employed instead. The term "17-ketosteroids" refers to those steroids possessing a ketone group on the 17th carbon atom. The principle 17-ketosteroids that occur in the normal human urine are androgenic. Therefore they serve in the female as an index of adrenal function.

In female hypogonadism, the 17-ketosteroids may be normal in primary ovarian failure but diminished if due to pituitary deficiency.

In considering endocrine therapy, functional amenorrhea and menorrhagia can practically be discussed together since both represent varying degrees of the same endocrine disturbance. To the woman suffering psychically from amenorrhea of functional origin, it makes no difference whether she is bleeding from a proliferative or a progestational endometrium. The mental relief is the same. To the woman, however, in whom amenorrhea and sterility coexist, the cure of the latter depends in great measure upon a physiological cure of the underlying uterine ovarian deficiency. We will therefore consider in order the specific therapeutic value of: (1) the gonadotropic hormones; (2) the estrogens; (3) progesterone; (4) androgens (testosterone); (5) thyroid.

1. *Gonadotropic Hormones*.—The gonadotropic hormones available are as follows:

(a) Hypophyseal Gonadotropin.—Extracted from fresh anterior



clinical usefulness than it is now, is a better understanding of the variations of the normal. The present war, in which so many electrocardiograms from normal young persons are being obtained and studied, is furnishing an opportunity in this connection that has never before existed.

Graybiel, McFarland, Gates and Webster<sup>8</sup> have recently analyzed the electrocardiographic findings in 1000 young aviators. Such changes as inverted T waves in Leads II and III and occasionally in chest leads, moderate S-T deviation in limb and chest leads, bundle branch block, particularly as a transient phenomenon following fright, QRS complexes of 0.11 and 0.12 second's duration and many other alterations were all found in these young aviators in whom no clinical evidence whatsoever of circulatory disease was shown. We quote the sound and important chief conclusion of the investigators: "The normal in electrocardiography extends well into what has been commonly regarded as an abnormal range."

Wolferth, Livezey and Wood<sup>25, 26</sup> have made further reports upon their studies on the distribution of potential differences produced by the heart to various portions of the body. These interesting and fundamentally important studies can be epitomized here only in the briefest way.

In precordial electrocardiograms, moving the exploring electrode only slightly considerably alters the tracing. This suggests that relatively small volumes of heart muscle produce potential differences on the overlying precordium that are individual and distinctive for these small volumes of heart muscle. These patterns of potential variation from many areas of the heart apparently are not widely distributed over the body surface. For example, the patterns found at positions  $C_2$ ,  $C_3$  and  $C_4$  undergo decrement very rapidly and are not recognized at positions at any distance from the heart. However, the patterns of potential variation produced by three areas of the heart muscle do not disappear, but are preserved, except for gradual decrement, at considerable distances from the heart. The pattern found at the  $C_1$  precordial position is present and as a rule not materially changed, except for decrement, along a line from the  $C_1$  position all the way to the right acromial process. That found at, or at least near, the  $C_5$  position remains relatively unchanged, except for decrement, all the way to the left acromial process. A third pattern, which Wolferth, Livezey and Wood name the diaphragmatic pattern, probably resulting from the potential differences produced by some area of the heart on the posterior or diaphragmatic portion of the ventricle, is widely transmitted to the body surface below the diaphragm, but only slightly distributed above the diaphragm. In this case decrement is slight.\*

\* The diaphragmatic pattern is not recorded by the usual chest leads. It can be recorded by placing the exploring electrode at certain positions below the diaphragm and also by an esophageal lead with the electrode below the auricles.

Secondary amenorrhea respond after the administration of 20 mg. of progesterone given daily for three days (Zondek). It is better, however, especially if the amenorrhea is of longer duration than six months, to prime the endometrium first with large doses of estrogen. Zondek recommends 1 mg. of alpha-estradiol given together with 10 mg. of progesterone daily for five days.

Progesterone may be of value in functional uterine bleeding if due to a progesterone deficiency such as is found in cases of hyperplasia of the endometrium. Ten mg. are injected twice weekly for the last two weeks of the cycle.

4. *Androgens*.—Testosterone may be given intramuscularly, sublingually, as a pellet under the skin or orally as methyl testosterone which is one-fifth as effective as the intramuscular injection. The danger of producing hirsutism should be kept in mind and may probably be avoided by limiting the dosage to 300 mg. per month and discontinuing it as soon as acne is evident. It is of great value in inhibiting some of the effects of estrogen on the endometrium and myometrium and in inhibiting the gonadotropic function of the pituitary. It tends to produce an atrophic endometrium. It is of special value, therefore, in functional uterine bleeding; 25 mg. are injected three times weekly.

5. *Thyroid*.—This is a valuable adjuvant in the treatment of functional amenorrhea and bleeding and may be used even when the basal metabolism is normal or slightly subnormal. The administration of desiccated thyroid tissue, 0.09 or 0.13 gm. ( $1\frac{1}{2}$  or 2 grains) daily, tends to increase cellular activity throughout the entire body, including the endocrine glands. In addition, it has been shown that thyroid extract neutralizes the action of estrogenic substance on the endometrium. This may explain the temporary beneficial effect of thyroid therapy in functional uterine bleeding when prolonged and unantagonized activity of estrogenic substance on the endometrium is the immediate cause of the abnormal uterine hemorrhage.

*Prostigmine* has been used in the treatment of delayed menstruation. One mg. is injected on three consecutive days. Estrogenic substances release acetylcholine in the uterus which produces local hyperemia. Prostigmine is a nonspecific agent with a similar property of potentiating the action of acetylcholine. If no menstrual flow occurs within seventy-two hours after the last injection a tentative diagnosis of pregnancy is made.

*Insulin*.—This drug may restore normal menstruation in some patients, especially those who are underweight and suffering with primary ovarian underactivity.

*Irradiation Therapy*.—Low dosage irradiation of the pituitary gland and ovaries is a valuable measure in the treatment of functional amenorrhea as well as menorrhagia of endocrine origin. The therapeutic action of irradiation is generally attributed to a transitory or permanent increase in cellular activity of the ovary. X-ray stimulation of the ovaries

of the shape of the heart in influencing the configuration of the limb and the precordial leads. This influence is due to the fact that the potential variations of the right arm are similar to the potential variations of those parts of the heart that are nearest to the right shoulder, and the potential variations of the left arm resemble the potential variations of those parts of the heart that are nearest the left shoulder, while the potential variations of the left leg are like the potential variations of the heart's diaphragmatic surface. An abnormal shape or position of the heart, e.g., vertical or transverse, may alter the normal transmission of potential variation to the left arm, right arm and left leg and thus alter the electrocardiographic configuration.

In this paper the electrocardiographic changes in left and right ventricular hypertrophy are also discussed and the detailed and specific changes that develop in these conditions in the chest leads are pointed out. The electrocardiographic changes seen in various types of bundle branch and intraventricular block are also shown. Wilson and his co-workers have already made an important contribution to practical electrocardiography in emphasizing the importance of the intrinsic deflection of precordial leads. They point out in this paper that the site of bundle branch block is best determined by comparing the time relation of the intrinsic deflection of leads obtained from different sites on the precordium with some fixed reference point, such as the peak or beginning of the R wave of Lead I. For example, in right bundle branch block the intrinsic deflection will occur later in relation to a fixed reference point in leads obtained from sites over the right ventricle, and earlier in leads made from points over the left ventricle. In left bundle branch block, the reverse of this relationship will be found. Undoubtedly both bundle branch block and ventricular hypertrophy can be more accurately studied by chest rather than indirect leads.

#### ROENTGENOLOGY

The term *mitralization of the heart* is often applied to a straightening or convexity of the left upper heart border, as seen in the postero-anterior roentgenogram. Shapiro<sup>13</sup> rightly objects to this loose term, chiefly on the ground that this state may be produced by many different factors or conditions and is not pathognomonic of a mitral valvular lesion.

The roentgen criteria of the diagnosis of *patent ductus arteriosus* assume considerable importance since this congenital lesion is now among the curable forms of heart disease. Donovan, Neuhauser and Sosman<sup>4</sup> have reported the important roentgen findings in fifty cases of patent ductus arteriosus, verified by operation. In order of frequency these are (1) dilatation of the pulmonary artery, (2) cardiac enlargement, (3) dilatation of the left auricle, (4) engorgement of the intrapulmonary vessels, (5) exaggerated pulsation of the left ventricle.

stitial type may be influential, but not to the same extent as those of the submucous variety. Subserous tumors, if small, do not cause bleeding, but if of large size, owing to pressure engorgement, abnormal hemorrhage may occur.

**DYSFUNCTIONAL UTERINE BLEEDING.**—Bleeding of endocrine origin is termed functional bleeding. This term is a misnomer. More aptly it should be called dysfunctional uterine bleeding. An interval shorter than sixteen days or a flow lasting more than eight days is abnormal. The endocrine organs most commonly responsible for excessive menstruation are the pituitary gland and ovaries. Thyroid dysfunction may, likewise, provoke free menstrual bleeding.

Functional menorrhagia is especially common (1) with the onset of puberty and (2) in the early menopause, although it not infrequently occurs in mature women under 40 years of age.

Functional menstrual disorders result from an ovarian failure. This may be primary due to inherent ovarian disease or secondary to extra-ovarian causes such as pituitary disease or other endocrine lesions or various types of constitutional disease. The approximate degree of ovarian involvement is indicated by the endometrium.

In patients with this symptom, uterine curettage usually reveals a hyperplastic endometrium characterized by a dense vascular stromal and epithelial overgrowth. The glands are large and cystic, representing the characteristic "Swiss cheese" pattern, large dilated glands being found side by side with others small and narrow. Many of these are lined by several layers of epithelial cells and show no secretion in the lumen.

Functional bleeding is usually due to deficient activity of the anterior pituitary lobe. This deficiency results in an imbalance of the two hormones of the ovary manifested by a prolonged production of the estrogenic hormone. This is associated with an absence or deficiency of the corpus luteum hormone. The abnormal development of the unantagonized follicle due to the failure of luteinization results in follicular cysts of varying size.

In the early menopause a certain number of women exhibit a tendency to menorrhagia or metrorrhagia. After eliminating carcinoma, myoma or polyps as causative factors by performing a diagnostic curettage, a functional origin must be considered. In these patients sclerotic changes in the ovarian parenchyma and the tunica albuginea render the follicle incapable of completing its cycle or of responding to a normal or even an increased pituitary function.

Occasionally, postmenopausal uterine bleeding is encountered, due probably to a temporary reactivation of the graafian follicle. This condition must be distinguished from granulosa cell tumors of the ovary which produce similar clinical and endometrial changes.

**Treatment of Functional Uterine Bleeding.**—In the treatment of bleeding of endocrine origin the mere removal of the hyperplastic endome-

number of factors other than right ventricular weakness may cause increased venous pressure

Warren and Stead<sup>20</sup> also feel that the old conception of congestive heart failure does not explain many clinical and experimental observations. These authors still accept the theory that the first event in chronic congestive heart failure is an impairment in the ability of the heart to propel blood forward. They believe that the first important result of this is not elevation of the venous pressure, but a decreased circulation through the kidneys and, as a consequence, improper elimination by these organs of salt and water. The water thus retained in the tissues produces edema, and in the blood vessels an increased blood volume. These processes ultimately result in a high venous pressure, but according to their theory edema is not the result of the elevated venous pressure, but a development that comes early and independently as a result of retention of salt and water through a kidney mechanism.

#### CORONARY ARTERY DISEASE AND ANGINA PECTORIS

One of the most important lessons that has already come out of the war is the frequency of *coronary occlusion* in young subjects, at least under the conditions of military life. An interesting report in this connection has been made by French and Dock<sup>7</sup> in which they record their experience in eighty fatal cases of coronary disease in soldiers between the ages of twenty and thirty-six years. An analysis of the clinical and pathologic features of these cases revealed that the disease occurred in men of various racial and national origins. The most striking presumable predisposing factor was overweight, which was present in 91 per cent of the cases. Vigorous effort, particularly when engaged in early in the morning, brought on the fatal attacks in over 50 per cent of the cases. Sudden death or the onset of the fatal attack occurred during sleep in only 10 per cent. The basis of coronary occlusion was found to be arteriosclerosis in all cases.

That *hypoglycemia* can produce various *cardiac manifestations* has been recognized. Harrison and Fink<sup>9</sup> attribute a variety of cardiac symptoms to "relative hypoglycemia," in which the blood sugar level is within the lower limits of normal or only slightly subnormal. The main reasons for attributing these symptoms to hypoglycemia are their appearance two or more hours after meals, their relief following the ingestion of glucose and their reproducibility by the administration of insulin.

White, Bland and Miskall<sup>22</sup> have discussed the prognosis in *angina pectoris*. Of 497 patients with angina pectoris, which they have followed, 445 are dead and 52 are living. The average period between onset and death in the 445 was 7.9 years, while the average duration from the onset of the disease in the living is 18.4 years. The average duration to date for the combined dead and living is nine years, which

but this should be employed only after ordinary means have failed. In the early menstrual life of women, only small doses of radium should be administered, and then, too, with extreme caution on account of the probability of inducing sterility or establishing a premature menopause. Temporary and even permanent amenorrhea may follow a 200 or 300 mg.-hr. dose. After the menopause, however, 600 to 1500 milligram-hours may be administered with impunity.

cedilanid apparently is absorbed three times as readily as oral preparations of digitalis purpurea. The most important therapeutic advantage of cedilanid is obtained from the intravenous preparation, primarily because of its rapid action. Approximately two and eight-tenths times as much drug is required for oral as for intravenous digitalization.

Several reports have appeared recently concerning the *toxic effects of intravenous mercurial diuretics*. Wexler and Ellis<sup>21</sup> discuss this problem and report two fatal reactions which came under their observation. Various nonfatal reactions to mercupurin are also described. These are divided into immediate and delayed types. Wexler and Ellis conclude that the fatal and immediate nonfatal reactions probably result from a direct toxic effect of mercury on the heart, whereas the delayed nonfatal reactions are incidental to the diuretic action of the drug. At present there is no known way of preventing occasional fatal reactions. Since mercurial diuretic drugs are valuable therapeutic agents in the treatment of congestive heart failure and since the frequency of severe or fatal reactions is low, the authors feel that the usefulness of these drugs outweighs their possible danger. They also point out that up to the present no fatalities have been reported after intramuscular injection of a mercurial diuretic and that the diuretic response often compares favorably with that which results from intravenous injection.

For some years, attempts have been made to develop a mercurial diuretic which can be given orally without toxic effect. Batterman, deGraff and McCormack<sup>1</sup> give their experience with such a preparation. They found in a group of forty-two patients, that mercupurin tablets administered orally were an effective and safe diuretic and, with proper use, are of definite value in the management of the cardiac patient with chronic congestive heart failure.

The results following *ligation for patent ductus arteriosus* are discussed by Shapiro and Keys<sup>14</sup>. Experience to date shows that ligation of the uninfected ductus can be performed with a resulting mortality of less than 10 per cent. Ligation of the ductus in the presence of subacute bacterial endocarditis offers an even chance of survival in the face of practically certain death without ligation. An analysis is presented of the results of 140 operations in which the ductus was ligated. Shapiro and Keys conclude that the majority of patients with patency of the ductus arteriosus should be operated upon after careful clinical studies have established the diagnosis. Ligation should be attempted immediately if subacute bacterial endocarditis develops.

Although Loewe, Rosenblatt, Green and Russell's<sup>10</sup> article is referred to last in this brief review, its position is no measure of the importance of the subject discussed: the *effects of penicillin in the treatment of bacterial endocarditis*. These authors report their experiences with penicillin in seven consecutive patients with subacute bacterial endocarditis, treated by a method which combined the use of penicillin and heparin. Further observation will be required to determine the perma-

hormonic influences as a supplemental cause. It must be remembered that basically the body develops from two corresponding embryonic segments and that the primary and secondary genital organs and structures develop from the müllerian and wolffian ducts which in turn have a common segmental embryonic origin. It is the influence of the primary genetic factor and the hormonal dominance activating the embryonic structures which determine the sexual normal or abnormal pattern. It is when there is some alteration from normal influences that we observe developmental anomalies, the most typical of which is hermaphroditism or pseudohermaphroditism.

#### HERMAPHRODITISM AND PSEUDOHERMAPHRODITISM

True hermaphroditism is rare and is characterized by an internal and external genital tract which is made up one-half of masculine structures and the other half of feminine structures. Externally the genital area shows a moderately developed penis and a testis and a rudimentary vagina. A pseudo-hypospadias exists in most instances, and also present are well-developed breasts. The hirsutic pattern may be heterosexual. The physical features are predominately feminine, however, the female appearing to respond psychologically to the dominance of the genital pattern. In such cases one cannot be guided exclusively by the hormonal assay in arriving at the final disposition of the case. It is a far safer procedure to request exploratory laparotomy, investigate the pelvic structures and be guided by the dominance of the internal anatomical development; provided the parent in the case of minors is fully appraised of the ultimate physiologic importance of Nature's own biologic reactions. In adults the problem is more complex because certain of these individuals have economically established themselves in one sex or the other. For example, a structurally developed adult female pseudohermaphrodite had established herself in a male occupation. She sacrificed her genital internal organs and proceeded in life as a male.

Such unfortunate states should be corrected as was done in the case of T.S., early in life, and who until age four years, was raised as a female. During hospitalization for a tonsillectomy and adenoidectomy, anomalies of the genital external tract were observed. These were an enlarged clitoris, abnormally large labia and imperforate vagina. Examination and closer inspection revealed that the labia had rudimentary rugae, the enlarged clitoris was an underdeveloped penis, the normally placed urethral opening for the female was actually a hypospadias, the imperforate vagina was actually a cleft type, anomalous scrotal development and careful palpation showed very small testes high in the inguinal canal.

In this instance we were dealing with a male in spite of the fact that the abnormal external genital structures resembled those of the female. A picture of the opposite type was obtained in the case of B.L., to be described presently, who had a greatly hypertrophied (male size) clitoris.



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of the clitoris was performed. Two years later the general body masculinization was still in progress, and was evidenced by increasing hypertrichosis, abnormal gain in height and muscular development, distinct masculine osseous build, abnormally deep pitched and raspy voice and regrowth of the clitoris to 2 inches in length and  $\frac{7}{8}$  inches in diameter. Erections of the clitoris occurred day and night and were extremely annoying. The right adrenal gland was found at exploration to be normal.

The referring gynecologist considered further surgery inadvisable and the patient was referred for medical therapy. During the past three years she has received practically continuously 0.5 to 1 mg. of stilbestrol daily with beneficial results. The clitoris has diminished 50 per cent in size, erections are inhibited as long as therapy is maintained, the voice pitch is gradually approaching feminine qualities, the hypertrichosis has been controlled and the general evolution of growth and psyche has distinct feminine trends. Vaginal discharge and breast development are not prominent. Intermittent therapy results in a return of clitoral erections and cessation of vaginal discharge and breast development.

Precocious puberty sometimes occurs in males with pineal tumors, but it has not been observed in females from the same cause. It is possible that intracranial lesions exerting pressure or invading the hypothalamic centers about the infundibulum may produce a precocious pubertal state. One of our patients developed precocious puberty, advanced osseous development and impaired vision at the age of five years. X-ray therapy produced satisfactory improvement. Ten years later the visual defect reappeared and progressed to the point that intracranial surgery was performed and a large pituitary cyst was evacuated. This patient has subsequently failed to develop either normal primary or secondary sexual characteristics. Presumptively her early precociousness resulted from the embryonic type of secreting cells contained in the Rathke pouch cyst and their subsequent degeneration, possibly as the result of the x-ray. Their subsequent replacement by cystic fluid produced a cure of the precociousness but also eventuated in complete sexual retardation.

#### PRECOCIOUS SEXUAL HAIR DEVELOPMENT

The appearance of hair in the pubic and vulvar regions and later the axilla is considered as an event indicating the approach of puberty. The premature appearance of hair in the female genital region is therefore of great concern to the child's parents and to the pediatrician. It is, however, a relatively rare condition, occurring in about 1 per cent of the female population. It is usually associated with precocious puberty, but may occur in isolation. The parents feared that precocious sexual development would occur. The physical, structural and mental development of the child was normal. Her intelligence, personality and psychological reactions were normal. She was a healthy, well-developed child. The premature appearance of genital and axillary hair and the precocious growth of the breasts appeared to be the only abnormality. The child was 5 years of age when the hair first appeared.

Likewise *inogastrone*, a somewhat similar substance that is present in human and canine urine and that is regarded by some authors as a metabolic product of enteogastrone, has now been employed in the clinic. Sandweiss and his co-workers,<sup>5</sup> who have found that it prevents experimental ulcer in the Mann-Williamson dog, have used it in sixty-three chronic duodenal ulcer patients with encouraging results. The beneficial effect was accomplished without significant change in gastric acidity and seems to be due in some way to stimulation of fibroblastic and epithelial proliferation and the formation of new blood vessels. Its clinical use, however, is limited at present because of the marked reaction produced at the site of injection.

**Jejunal Transplant into Stomach Wall**—Another procedure in the management of peptic ulcer that has grown out of the experimental laboratory has been suggested by Lord, Andrus and Stefko. They<sup>6, 7, 8</sup> had previously shown that the transplantation of a portion of the upper jejunum into the stomach wall of the dog by means of a pedicle graft produces a decrease in gastric acidity, in addition, that it causes a reversal of the response to histamine—a diminution of hydrochloric acid rather than an increase. At the same time they found that a duodenal transplant is considerably less effective and an implantation of mucosa from the ileum or transverse colon totally ineffective, also, that an accompanying gastro-enterostomy counteracts the effect of the jejunal transplant. More recently they<sup>9</sup> have found that such a jejunal transplant prevents the experimental production of ulcer and that in dogs that have already had ulcer induced by the injection of histamine phosphate in beeswax and liquid petrolatum, it causes clinical improvement and even healing of the ulcer despite the continued injection of the histamine mixture.

They<sup>10</sup> have reported the application of this method of ulcer prevention and treatment in four cases of intractable ulcer in man. All showed a favorable clinical response and two had a definite decrease in gastric acidity. The third case was reported too soon after operation to permit laboratory evaluation and in the fourth case postoperative gastric analyses were impossible because of an uncooperative patient. This distinctly new surgical approach in the treatment of peptic ulcer warrants further study.

**Sodium Alkyl Sulfate**—Shoch and Fogelson<sup>11, 12</sup> have introduced another medicinal product in peptic ulcer treatment—sodium alkyl sulfate. They claim that this drug, a combination of sodium lauryl, palmityl, oleyl and stearyl sulfates, inhibits peptic activity with no coincident change in the pH. By its frequent administration they state that they were able to increase by as much as 170 days the survival time of dogs receiving injections of histamine phosphate in beeswax and liquid petrolatum. They gave the drug to thirty-four patients with intractable ulcer and reported good results in twenty-six of them.<sup>12</sup> Kirsner and Wolff<sup>13</sup> corroborated the fact that sodium alkyl sulfate tem-

part of the general body growth and is produced by the combined influences of the anterior pituitary growth hormone and thyroid hormone. The loss of this synergistic hormonal effect is well demonstrated in the cretin. Thyroid hormone is very essential to the normal development of all cells and particularly those cellular changes which are concerned with the higher functional capacity; the reproductive cells and tissues are definitely in this classification. Thus many functional disorders of the internal genital organs are the result of early or later acquired thyroid or anterior pituitary deficiency and in the adult range from sterility to metrorrhagia. Therefore, in subnormal developments of the genital tract and retarded genital functional development we must investigate for anterior pituitary and thyroid deficiencies as well as a deficiency in the anterior pituitary-gonadal axis. The general features of this type of disorder are compositely represented in pituitary infantilism and often persists to adult life producing a major psychological and sociological problem.

D. H., an unmarried woman 24 years of age, typifies this clinical problem. Since the age of 12 years she had sought treatment for her statural and sexual underdevelopment. She is 57 inches tall, weighs 113 pounds, and the relationship of the lower measurement, span and height are proportionate. The wrist formation is atypically achondroplastic. Mentally she is depressed, chiefly because of the primary amenorrhea, infantile genitalia, very deficient pubic and axillary hair and absence of breast development. The thyroid was small and doughy soft in texture such as is found in the secondary type of hypothyroidism.

In general a therapeutic regimen for this patient appeared to be futile, nevertheless a therapeutic program was instituted to stimulate breast development and general tissue response. The therapy consisted in the administration of estinyl (Schering) 0.05 mg. nightly and the twice daily administration of a capsule containing 1 grain of anterior pituitary,  $\frac{1}{8}$  grain of thyroid, U.S.P., and 2 grains of calcium glycerophosphate. In one month a mass about the size of a half walnut was felt beneath both nipples. The estinyl was reduced to every third night. In two months the breast tissue had developed to the size of half a small lemon, uterine bleeding first appeared at this time and persisted for thirty-six hours. One month later on June 8, 1945, a normal five-day menstrual period occurred and the breasts were the size of half a medium orange. The psychological change in this patient is solely due to her breast development and the appearance of the (therapeutic) menstrual flow.

The role of the adrenal cortex, pineal and thymus glands in genital development is not too clearly defined. We do know that hyperfunctional adrenal cortical states do have a depressant effect upon ovarian development and function. The ovaries in this disorder show diminished size and atretic follicles and because of diminished estrogen production, the breasts and the uterus are small.

#### VIRGINAL GYNecomASTIA DUE TO INCREASED SENSITIVITY OF END ORGAN TO HORMONIC STIMULATION

Recently another factor has entered the field of discussion of growth development—the factor of the sensitivity of the tissue end organ to

ing Approximately 125,000 persons die each year in the United States from gastric cancer,<sup>17</sup> more than from any other malignant disease, and, according to the Mayo statistics, as reported by Walters, Gray and Priestley,<sup>18</sup> 43 per cent of the cases of gastric cancer are inoperable when first diagnosed. In their series they found that 22 per cent of those subjected to surgery were in a hopeless condition and in an additional 19 per cent, nothing more than a palliative procedure could be carried out. Thus in only 25 per cent of their series was the lesion resectable and a mere 6 per cent of the original group was alive five years after the diagnosis was made.

**Roentgenologic Diagnosis in Early Stages**—The mortality as stated is far too high for a condition that is potentially curable, when diagnosed in its early stages. Such an early diagnosis, furthermore, is usually possible if a roentgenologic investigation is made with the onset of symptoms. St. John, Swenson and Harvey<sup>19</sup> have gone even further in advocating a rapid routine roentgen study of persons without symptoms. They examined 2432 people over fifty years of age who came to a New York hospital either as visitors or because of complaints not associated with the gastro-intestinal tract. These subjects were fluoroscoped after taking barium by mouth and in the first 1000 examinations one film also was made, but since this latter procedure contributed no additional information it was then discontinued. The time for each examination was approximately one minute and the cost per person, excluding only the radiologist's fee and the overhead on the roentgen equipment, was 48 cents. Admittedly the results in such a superficial study are only as good as the roentgenologist himself, but in their total group three surgically proved gastric malignancies were discovered, one of them so obscure in its manifestation that it was overlooked at the first operation and another so small that it became one of the earliest gastric carcinomas ever removed in that hospital.

Thus roentgenologic study of the stomach is a practical procedure in the routine investigation of large groups of the population and, if employed intelligently, may lead to the recognition of cancer of the stomach when it is easily curable. Even if resorted to only after the development of the earliest digestive symptoms it will result in the saving of many lives. Little more can be expected in the perfection of surgical technic, but earlier diagnosis offers the possibility of a marked reduction in the mortality from this disease.

#### GASTRITIS

Correlation of the descriptions of the subjective and of the objective evidences of gastritis is difficult. From the maze of clinical and gastroscopic observations, only two groups of cases emerge in which symptomatic, endoscopic and pathologic reports show any semblance of agreement. One of these is *hypertrophic gastritis*, and Gordon<sup>20</sup> has found that approximately half of the patients with this type have a

sensitivity of the end organ to hormonal stimulation, are unilateral virginal gynecomastia, excessive statural development and incipient hypertrichosis.

**Virginal Gynecomastia in a Female Infant Aged 18 Months.**—Premature development of the breast may occur as early as one year. It may be present as a unilateral or bilateral abnormality but it occurs more frequently as a bilateral state.

In P. M., a female infant aged 18 months, breast development was first observed at the age of 1 year. The breast tissue developed rapidly in both mammary regions and at times appeared to cause the infant discomfort (Fig. 179). During the past few months no increase in size of the breast has been noted. The birth weight was 8 pounds 2 ounces, the height 26 inches. First dentition occurred at 4½ months and the infant walked at 10½ months. At present the height is 33 inches, lower measurement 14½ inches. Sixteen teeth are present. The breasts are 2½ inches in diameter and 1½ inches deep. The breast parenchyma is 1½ by ¾ inches. The nipple and areola are developed. The breasts appear to be sensitive. The external genitalia are of normal size for age. A vaginal discharge has been observed.

While I believe that in most instances, whether it occurs in the female or the male, gynecomastia is a condition of increased sensitivity of the end organ of the breast cell to estrogenic stimulation and is not amenable to *rational* endocrine therapy which considers the body tissues as a complete functional unit, this disorder should not be dismissed as such until granulosa cell tumors of the ovary are excluded by hormonal assay and complete physical and clinical investigation. Besides producing premature breast development, granulosa cell tumors and luteoma also produce premature feminization and uterine bleeding because such tumors produce excessive and demonstrable amounts of estrogen (estradiol).

#### HYPERTROPHY OF THE BREAST

This condition is similar to virginal gynecomastia and may be unilateral or bilateral and may or may not be associated with signs of painful engorgement preceding the onset of the menarche or premeneses. For the painful engorgement I am opposed to the use of male hormone in young females. A more practical and harmless treatment is to stimulate urinary excretion and deplete the system of the estrogen by the use of a saline diuretic and fruit juices. A special brassiere or one that uplifts the breasts, particularly on the axillary side, should be worn.

Plastic surgery is the only means of correcting unilateral or bilateral hypertrophy of the breast if the overdevelopment of the breasts is producing physical discomfort or psychologic reactions. However, before this is definitely decided upon it is well to remind the patient that their present size, which she feels she cannot tolerate, may be an asset during later years when breast atrophy normally occurs. This

military hospitals in Great Britain, 55 per cent had peptic ulcer. Naval statistics<sup>28</sup> show that in 1924 the admission rate for this disease was only 69 per 100,000, while today it has more than doubled that figure. In 1942, according to Hogan,<sup>20</sup> 2496 naval personnel were hospitalized for peptic ulcer, 1974 of the group having had a history of ulcer before coming on active duty.

This marked increase in peptic ulcer during the present war was totally unexpected, and Tidy<sup>20</sup> states that at first two theories were advanced in explanation of it: one, that an error had been made in the diagnosis and the other, that the poor army food was responsible. Both have subsequently been proved incorrect in the light of further study. The diagnoses were accurate, the food on the whole is much better than it was in 1914-18. As a matter of fact, despite improvement in the food during the past year or two, the incidence of ulcer has not lessened.

The increased incidence of ulcer in the armed forces has been coincident with a similar trend in the civilian population. This was particularly apparent during the period of intense bombing of Britain, when in Bristol, Wolley stated,<sup>30</sup> the number of cases of perforated ulcer admitted to the hospitals increased 15 per cent over the number admitted in times of peace. Many of the service men, in fact, had developed their first symptoms while still in civilian life. Chamberlin<sup>23</sup> reported that 96 of 139 enlisted men had their first symptoms prior to military life. These facts lead one to suspect that the marked increase in peptic ulcer among the officers and the enlisted personnel is on the same basis as for civilians, both being connected in some way with the strain and anxiety that are necessarily a part of any war.

The disposition of army and navy personnel in whom an accepted diagnosis of ulcer has been made constitutes a considerable problem. The tendency at first was to return most men to duty after their symptoms were relieved by medical treatment, but the distressing frequency of a recurrence, requiring repeated hospitalization, has caused a change in policy. At present the practice in both our forces and those of the British is to invalid from service all men with an established diagnosis of ulcer except for certain specially trained and irreplaceable persons.

**Gastritis**—Gastritis in the United States Army and Navy, as elsewhere, has been frequently diagnosed only since the gastroscope has come into more general use. For this reason, some of the earlier articles mention it briefly if at all and undoubtedly include many such patients among the functional or neurogenic cases. At the station hospital at Camp Blanding, Florida, Annis<sup>25</sup> reported that 276 patients were gastroscoped in the two years preceding May, 1943. One hundred and nine, or 39.5 per cent, of these showed some form of gastritis. Gold,<sup>31</sup> on gastroscoping fifty patients at another army hospital, found a comparable figure, namely 36 per cent. McGlone,<sup>32</sup> in an analysis of

## USES AND ABUSES OF ENDOCRINE THERAPY

JACOB HOFFMAN, M.D.\*

ENDOCRINOLOGIC research continues to increase our knowledge of gonadal and reproductive physiology and add to the number of diagnostic technics and potent hormonal preparations useful in gynecologic disorders. The physiologic and diagnostic aspects of gynecic endocrinology still remain vague and confusing to many practitioners, but all have found within their grasp the numerous biologically potent sex hormones now available for clinical use. It is easy to understand their eagerness to employ these substances in the treatment of amenorrhea, uterine bleeding, dysmenorrhea, habitual abortion, sterility and other gynecologic disorders which have so long baffled the clinician. Unfortunately, when they turn to the medical literature for guidance in the application of these hormones, they are soon bewildered by the widely divergent views expressed by apparently equally competent investigators. Some maintain that organotherapy deserves a prominent place in the treatment of functional gynecologic disorders, while others insist that its sphere of usefulness is limited and its efficacy questionable.

While many of the more optimistic reports are undoubtedly in good faith, they cannot be accepted at face value either because of their failure to use controls, or to take into account the fact that a large percentage of such disorders, particularly in younger women, are subject to spontaneous correction or respond readily to general hygienic measures and psychic suggestion. The psychotherapeutic effect of organotherapy, especially where the hypodermic route is used, should be borne in mind when evaluating the results of treatment. In following the evolution of organotherapy, one is struck by the fact that brilliant results have been reported at one time or another in virtually all disorders affecting the sexual sphere, with all the sex hormones, given singly or in combination, whether in relatively inert or potent form, and whether given in large or ridiculously small doses. Investigators reporting favorable results have often been led by their subsequent experience to modify or reverse their original judgment. Unfortunately, this may either fail to come to the practitioner's attention or be obscured by persistent allusions to the original favorable reports, contained in the pharmaceutical literature which reaches him at frequent intervals.

Some general practitioners and even some gynecologists, acting in good faith, continue to employ organotherapy after doubt has been cast on its efficacy, because they are loathe to relinquish one therapeutic weapon before another is offered to take its place. Their "give it anyhow" attitude is justifiable only if the treatment is certain to be harmless, and the thought that something concrete is being done is

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\* Associate in Gynecology, Jefferson Medical College; Pathologist in Gynecology, Jefferson Medical College Hospital, Philadelphia.



not yet been determined, but certain experimental results seem to indicate a virus agent its transmissibility in serum, its lack of visibility under the microscope, its passage through bacteria-retaining filters and its persistence in serum-chick embryo media<sup>34</sup>

Clinically the attacks of epidemic hepatitis, as described by Turner and his associates<sup>35</sup> and by Greene,<sup>36, 37</sup> were remarkably similar regardless of their geographic location After an incubation period of eight to twelve weeks mild prodromal symptoms of anorexia, weakness, lassitude, abdominal distress and occasional vomiting were noted At this stage the disease was not infrequently misdiagnosed as gripe In some patients these symptoms disappeared with the appearance of the jaundice and in most patients they regressed during the first week of hospitalization Fever was unusual, as were pruritus and bradycardia Leukopenia was common

On physical examination the usual discoloration of the skin, serous and mucous membranes was observed In addition, the liver was enlarged and tender in approximately one fifth of the cases although it might have been palpable in a larger number had it been possible to examine them throughout the entire course of their illness Weight loss was almost invariably present and was most pronounced in the severe cases The icteric index ranged from 15 to 200, and hepatic function tests indicated various degrees of impairment The response of the commonly prolonged prothrombin time to vitamin K therapy was of clinical significance in that the more severe cases responded poorly if at all, while the milder ones returned to normal in a few days

The complications included nervous system disturbances, ascites, hemorrhages into the skin and mucous membranes and, in the late stages, a secondary anemia Except for the petechial hemorrhages, the complications were most often seen in the fatal cases and will be discussed more fully below

In general, recovery occurred in four to eight weeks Lucké,<sup>38</sup> in analyzing pathologic material from fourteen cases that came to autopsy or operation for some incidental reason one to fourteen months after clinical recovery from their hepatitis, found evidence indicative of complete restoration of the liver to normal Grossly there were no abnormalities of that organ The microscopic appearance varied somewhat depending on the length of time between the attack of hepatitis and death or biopsy The livers of those patients who died during convalescence showed only partial repair in that small patches of parenchyma were still lacking in the center of the lobules but at the same time many multinucleated hepatic cells indicating active regeneration were present Those who died one month or more after the attack of hepatitis showed complete restoration of the liver parenchyma with no scarring This was to be expected, according to Lucké, because the parenchyma of the liver has long been known to possess great power of regeneration and his other studies of fatal cases had showed that

from normal. The large majority of cases encountered in the gynecologic clinic fail to show deviations sufficiently striking to be significant or conclusive. Where a marked deviation is encountered, its interpretation may present difficulties, due to our incomplete understanding of the factors controlling the level of the sex hormones in the body fluids. The rates of production, utilization, conversion or destruction of the hormones are only a few of the variables which may affect the results.

In my experience and that of others,<sup>9</sup> the most reliable and significant information is provided by histologic examination of endometrial curettings. This procedure will disclose organic lesions of the uterine cavity and in addition may provide a clue to the functional status of the ovary and its governing gland, the anterior pituitary. A thorough physical examination in the nude, with particular attention to the developmental status of the genitalia and secondary sex characters as well as the presence of endocrine stigmata, may also yield valuable information.

The hormones now on the market for the treatment of functional gynecologic disorders include the gonadotropins derived from anterior pituitary gland tissue, human pregnancy urine (chorionic gonadotropin) and serum of pregnant mares (equine gonadotropin); natural and synthetic estrogens; progesterone and pregnenolone; and natural and synthetic androgens. Space permits only a brief discussion of the disorders for which these substances have been recommended; the theories advanced to justify their use; and the possible beneficial and harmful consequences of their use.

#### FUNCTIONAL UTERINE BLEEDING

The sex hormones are widely used for the control or cure of functional uterine bleeding, particularly that associated with endometrial hyperplasia. Progesterone<sup>10</sup> and the orally active progestational substance, pregnenolone,<sup>11</sup> have been advocated on the assumption that they will override the effect of the endogenous estrogens on the uterine mucosa and thus prevent excessive mucosal proliferation and bleeding. Some believe these substances inhibit the myometrial contractions and thus reduce the rate of blood flow to the endometrium. Evaluation of their efficacy in uterine bleeding is difficult because of the frequent tendency to spontaneous coagulation and the possible curative effect of other measures. Such as curettage, often performed on a diagnostic purpose.

Estrogen administered cyclically either alone or with progesterone is advocated by some workers<sup>12,13</sup> who attribute its apparent beneficial effect to its ability to alter the functional capacity of the endometrial blood vessels. In the author's opinion, there would seem to be no rational basis for the use of this hormone in a condition where it is

it became more common later in this stage. During the final period, shrinkage of the liver was the rule.

The liver in all of the fatal cases examined by Lucké was characteristic of so-called idiopathic acute yellow or red atrophy. Grossly it was usually decreased in size but this varied somewhat with the duration of the disease, the smallest livers being found when the course of the disease was shortest. Characteristically the involvement of the liver was not uniform. Pale green or ivory colored nodules of various sizes, due to parenchymal proliferation, projected above the surface in some areas, contrasting with sunken gray or dull red patches where the parenchyma had been destroyed. On the cut surface the same irregular distribution was obvious. The pale green, ischemic and bile-stained regions with their distinct lobulations were very different from the dark red areas with their indistinct landmarks and with blood oozing from the cut surface.

This variability characteristic of epidemic hepatitis was also noted on microscopic examination. Sections from the red areas showed complete destruction of the liver parenchyma with the lobules still outlined by small proliferating bile ducts and the sinusoids and reticular framework still present. The dead cells usually had been removed, so that scarring did not result, but inflammatory cells, some of which contained lipofuscin, were found. Sections from the yellow nodules showed hyperplasia of the parenchymal cells with the formation of atypical lobules that rarely resembled normal liver tissue. No inclusion bodies, such as occur in yellow fever, were found. As indicated above, many of the intralobular bile canaliculi were plugged with debris.

#### CEPHALIN-CHOLESTEROL FLOCCULATION TEST

Further experience with the cephalin-cholesterol flocculation test has tended to confirm Hanger's original belief that it is an aid in differentiating obstructive from hepatocellular jaundice. The technic is relatively simple, but the test apparently is easily influenced by a number of factors and therefore must be well controlled to eliminate falsely positive reactions. Neefe and Reinhold<sup>40</sup> have recently pointed out that some of these false positives may be eliminated by protecting the saline-serum-antigen mixtures and the individual reagents from bright light. Variation in the sensitivity of the cephalin-cholesterol complex is another source of error and makes it necessary to compare each new lot with a mixture of known reactivity if uniform results are to be obtained. They also have noted that changes in temperature lead to variable reactions and that more reliable results seem to be obtained between 20° and 25°C than at 37.5°C. The optimal temperature, however, has not as yet been determined.

In spite of some discrepancies, most of the workers in this field, including Yardumian and Weisband,<sup>41</sup> Clay and Moore,<sup>42</sup> Nadler and Butler<sup>43</sup> and Hanger,<sup>44</sup> have found that the test gives definitely positive

action of this hormone on the human ovary. Goldzieher<sup>20</sup> believes it acts at least partly by suppressing a hypothetical bleeding factor which increases bleeding from the endometrial capillaries. It remains to be seen whether carefully controlled studies will establish the lactogenic hormone as a useful aid or throw it into the discard along with chorionic gonadotropin, which was also once credited with brilliant results in functional uterine bleeding.<sup>21</sup>

On the whole, organotherapy would seem to have only a limited sphere of usefulness in this disorder. In the adolescent, the condition is often self-limited and will eventually correct itself without treatment. In women of child-bearing age, curettage alone, repeated if necessary, is often effective.<sup>22</sup> The gonadotropes should be avoided because of the uncertainty of their action and the danger that they may have a disrupting influence on an already disturbed ovary. Thyroid therapy is often useful, particularly where the basal metabolic rate is depressed. For bleeding during the late reproductive, menopausal and postmenopausal epochs, organotherapy is unnecessary, for radiation or surgery is the therapy of choice and may be resorted to without hesitation at this time of life. Endocrine therapy is not only an unnecessary expense, but if used without a thorough examination to exclude organic lesions, as is often the case,<sup>3</sup> it may cause dangerous delay in the diagnosis and treatment of pelvic carcinoma.

#### AMENORRHEA

Since amenorrhea may result from any one of a number of causes, organic as well as functional, a careful investigation to determine the nature of the underlying disturbance is an essential prerequisite to effective treatment. Unfortunately, a search for the cause is too often subordinated because of the many bold claims that this or that sex hormone is all that is needed to combat the amenorrhea. This attitude is to be deplored, for systemic disease is often overlooked in the rush to apply the sex hormones.

Both the gonadal and gonadotropic hormones have been employed extensively for the treatment of primary and secondary amenorrhea. It is well established that the ovarian sex hormones, if given in adequate amounts over a period of two to three weeks, can develop the human uterine mucosa to the point where cessation of treatment will be followed by bleeding from an estrogenic or progestational type of endometrium, depending on whether estrogen alone or estrogen plus progesterone is used.<sup>23</sup> In some cases, as first shown by Zondek,<sup>24</sup> withdrawal bleeding may be induced by administering progesterone, either alone or with a small quantity of estrogen, on two successive days. Episodes of withdrawal bleeding can be induced at regular intervals as often as the patient's pocketbook will permit. Such treatment is contraindicated where the amenorrhea represents the effort of a depressed organism to conserve its depleted resources. Though the oc-

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Of interest is the observation of Whitacre and Barrera<sup>25</sup> that amenorrhea occurred in 14.8 per cent of the women of menstrual age interned at Santo Tomas in Manila. In many of the cases, the menses stopped abruptly either immediately after the first bombing of Manila or shortly after internment and too soon to be attributable to nutritional deficiency. These observers conclude that psychic shock, worry and especially fear were responsible. Hormone studies revealed a deficiency of estrogen associated with normal or possibly excessive quantities of gonadotropin. They suggest that the shock caused amenorrhea by suppressing ovarian function through the mediation of the autonomic nervous system. Most of the women had a spontaneous return of normal periods after a few months. Gonadotropin therapy was withheld because of the positive gonadotropic hormone tests. Sex hormones were not available. For want of something better, vitamin E, which happened to be on hand, was given in doses of 20 drops three times a day for ten days. Eight of ten patients so treated experienced a flow at the end of treatment. Since there is no reason to expect stimulation of the generative tract from such therapy, Whitacre and Barrera assume that the good results were mainly due to its psychotherapeutic effect.

Where the cause of the amenorrhea is a nutritional deficiency, a well-balanced, vitamin-rich diet is often effective, while amenorrhea associated with obesity often responds to reduction of weight through dietotherapy. Small doses of thyroid are a useful adjunct in the treatment, particularly where the basal metabolic rate is low. The use of any metabolic stimulant is contraindicated, however, where the low basal metabolic rate is associated with nutritional deficiency or some other constitutional depressive state, for here it apparently represents an effort of the organism to conserve its waning resources.

#### DYSMENORRHEA

Menstrual pain in the absence of demonstrable pathologic change has long baffled the gynecologist. An endless number of theories have been proposed and equally numerous remedies tried for its relief or cure. Recent evidence suggesting a possible endocrine basis has encouraged the wide use of organotherapy. The reported results have been inconstant and are difficult to evaluate because of the important part played by the psyche in this condition. Confusion arises from the fact that equally good results have seemed to follow opposite forms of treatment, while both good and bad effects have been described after identical therapy. Thus far, a significant advantage of endocrine therapy over general hygienic measures and psychotherapy has not been convincingly demonstrated.<sup>26</sup>

Some observers employ progesterone<sup>27</sup> or pregnenolone<sup>28</sup> with the aim of inhibiting myometrial contractions and promoting the excretion of the motility-stimulating hormone, estrogen. Others oppose this form of treatment on the ground that pain is associated with a pregravid type of endometrium and can be prevented by measures calculated to prevent corpus luteum formation and conversion of the endometrium to the pregravid phase. They reason that progesterone may be expected to aggravate rather than allay menstrual pain. In their

# TREATMENT OF THYROTOXICOSIS WITH THIOURACIL

KARL E PASCHKIS, M D \*

SULFONAMIDES, thiourea and related compounds have been shown to be goitrogenous in experimental animals<sup>1, 2</sup> Analysis of this action revealed that the metabolism of the animals was decreased At the same time the thyroid glands showed the histologic picture of maximal stimulation The histologic structure of the pituitary glands was identical with that seen after thyroidectomy Administration of iodine did not prevent the changes following the administration of these drugs The latter were, however, incapable of counteracting injected thyroxin

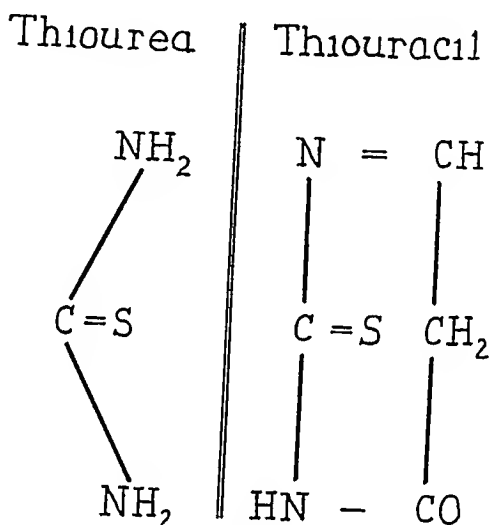


Fig 105

From these experiments the conclusion was drawn that these drugs inhibited formation of thyroid hormone This "chemical thyroidectomy" releases the pituitary gland to oversecretion of thyrotrophic hormone which in turn produces hyperplasia of the thyroid gland Hence the paradoxical picture of hyperplastic thyroid glands associated not with hyperfunction but contrariwise with hypofunction

The mechanism of the inhibition of formation of thyroid hormone is not yet fully clarified Experiments using radioactive iodine as tracer substance<sup>3, 4</sup> have shown that thyroid glands under the influence of

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From the Endocrine Clinic and the Department of Medicine and of Physiology, Jefferson Medical College and Hospital

\* J E Mears Fellow in Medicine and Physiology and Associate in Medicine and in Physiology, Jefferson Medical College, Chief of Endocrine Clinic, Jefferson Medical College Hospital, Philadelphia

The estrogens have been employed with the aim of developing a hypoplastic uterus, enlarging the tubal lumen, altering the cervical secretions so as to make them more permeable to the ascending sperm, or modifying the vaginal secretions so as to provide a more favorable medium for the deposited sperm. Unfortunately, the dosage required for these effects is sufficient to inhibit ovulation, an effect which is obviously undesirable where fertility is the main objective.

Administration of a potent gonadotrope capable of inducing normal cyclic changes in the ovary would seem to be rational therapy in sterility due to deficient oogenesis, secondary to anterior pituitary hypofunction. Such a deficiency may exist not only in women with amenorrhea or irregular uterine bleeding, but also in those who have apparently normal flows at monthly intervals. The occurrence of anovulatory cycles in such women is now generally conceded, though estimates of their incidence vary widely. In a recent study, Sharman<sup>37</sup> found such cycles in 6.4 per cent of 358 cases of primary sterility. It is regrettable that the available gonadotropes, in their present form and with the existing limitations on our knowledge concerning their proper application, are of little value and may even do harm in such cases.

There is evidence that with proper control of dosage and timing, ovulation may be induced with gonadotropic substances in the monkey,<sup>38</sup> cow<sup>17</sup> and other species. In the human ovary, the response to similar therapy has thus far been disappointing. Typical is the report of Wilson,<sup>39</sup> who used equine gonadotropin for sterility and at first got results which appeared most encouraging but, in the light of his subsequent experience, proved to be pure coincidence. The ability of the gonadotropes to induce ovulation in the hypofunctioning ovary has not yet been convincingly demonstrated. When brought to bear on ovaries which show some degree of function, they induce alterations which quickly pass the limits of the physiologic. For example, Davis and Hellbaum<sup>40</sup> found that in normally menstruating, pregnant and postpartum women an extract of sheep anterior pituitary gland tissue produced marked enlargement of the ovaries, increasing their size ten to twenty-fold. The proliferative changes thus initiated eventuated in the formation of large follicles and follicle cysts. Except for three pregnant women who appeared to have ovulated just prior to laparotomy, performed following administration of the extract, none of the subjects showed evidence of ovulation or corpus luteum formation.

Equally unphysiologic effects have been described following equine and chorionic gonadotropin given in succession,<sup>7</sup> and anterior pituitary and chorionic gonadotropin administered simultaneously in the form of Synapoidin.<sup>8, 16</sup> Davis<sup>8</sup> observed multiplication of corpora lutea and hemorrhagic follicles with much edema and interstitial hemorrhage and occasionally formation of a single large cyst. According to this observer, these changes occur rapidly but regress slowly. In some of his cases several months passed before the ovaries returned to normal size. He points out that such tumors are liable to the general risks of complications such as hemorrhage and torsion, and call for careful supervision during treatment.

It is to be hoped that proper control of dosage and timing will eventually make it possible to avoid these undesirable effects. For the present, however, these substances should be used with caution because



thiouracil in serum, urine, tissue extracts and body fluids all employing Grotes' reagent<sup>10, 11, 12, 13</sup> Williams et al have made extensive studies of thiouracil levels of the serum and urine and of the tissues We<sup>14</sup> have found the method of Williams et al unsuitable and have employed Chesley's method<sup>13</sup> with minor modifications in our studies The curves in Figures 106 and 107 show the serum levels after ad-

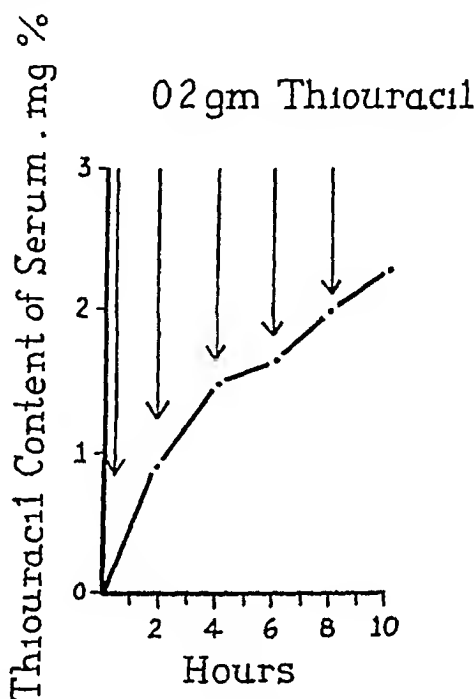


Fig 107—Thiouracil level in serum after 1 gm of thiouracil was given in five divided doses of 0.2 gm each at two-hour intervals Note the gradual increase and more nearly uniform levels as compared to the curve in Fig 106

ministration of 1 gm in one dose and in five divided doses of 0.2 gm each respectively Excretion is rapid, between 22 and 48 per cent being recovered from the urine within twenty-four hours Twelve to sixteen hours after the last of the divided 0.2-gm doses no thiouracil or only traces can usually be detected in the serum

#### THERAPEUTIC USE OF THIOURACIL

Several reports on the use of thiouracil in the treatment of thyrotoxicosis have been published<sup>8, 9, 15, 16</sup>

The drug is given orally The daily amount is given in several divided doses We have used 1 gm daily, divided into five equal doses of 0.2 gm given every two to three hours We have employed this type of treatment in the initial management of every case irrespective of the severity Others have used somewhat smaller doses, 0.6 gm in two to three divided doses

I have reached the conclusion that general hygienic and medical measures calculated to put the patient into the best possible physical and mental state are to be preferred. Thyroid therapy is of value where the basal metabolic rate is low or fails to show the usual rise with the advance of gestation.<sup>49</sup> Where abortion threatens, rest in bed, mild sedation and avoidance of coitus, purgatives and undue excitement would seem to be as effective as any other form of therapy thus far proposed.

### THE CLIMACTERIC

Before attempting to pass judgment on the rationality or efficacy of any form of treatment recommended for the relief or cure of the climacteric symptom complex, it is important to bear in mind that it is an expression of a general nervous and endocrine upheaval, possibly precipitated by the decline of ovarian function. The nature, intensity and duration of the symptoms apparently depend on the severity of this upheaval and the reaction of the organism to the altered hormonal and nervous environment. This in turn depends on the previous status of each system and the extent to which it is implicated in the general regression which heralds the approaching senium. Since aging and ovarian regression are inevitable and irreversible processes, it is obvious that no form of therapy can do more than ease the patient through this critical epoch.

Sex hormones, particularly the estrogens,<sup>50, 51</sup> have achieved their greatest popularity in the treatment of the vasomotor and other annoying symptoms associated with the menopause. Even those who have maintained an attitude of cautious skepticism regarding their value in menstrual and reproductive disorders, have permitted themselves to become enthusiastic concerning their use for this purpose.

The degree of the enthusiasm for estrogenic therapy in the menopause varies: some find the estrogens effective only for the control of flushes, while others claim good results in a variety of conditions including kraurosis vulvae, arthritic pains, intestinal symptoms, hypertension, edema, hyperglycemia and glycosuria, respiratory and circulatory disturbances, dysuria and incontinence, and involutional melancholia. Since gonadal involution with consequent estrogen withdrawal is only one of many physical and psychological changes incident to the aging process, it is difficult to conceive how mere substitution of estrogen can relieve or control the complex symptomatology. In view of the large component of psychosomatic manifestations associated with this epoch, it is entirely possible that the brilliant results attributed to estrogen therapy are in large part due to its psychotherapeutic effect. It is significant that many menopausal women are relieved by reassurance, alone or with sedation,<sup>52</sup> and often respond to placebos. Of interest in this connection is Frank's observation<sup>53</sup> that oral estrogen therapy, which relieved most of his patients, was without effect in a few who had convinced themselves that estrogen by this route is ineffective. If it is granted that a patient's psychic convictions can prevent her from responding to estrogen therapy, one cannot help but suspect that favorable responses, where noted, were due to the psychic conviction that the therapy would be effective.

0.1 to 0.3 gm daily. This corroborates the experience of others. We have used the word "permanent" in quotation marks because the present experience with this treatment has not been sufficiently long to determine just how permanent the beneficial effect will be.

**CASE I—M B**, a white man aged forty-one years, complained of weight loss, increased appetite, weakness, nervousness, excessive sweating, subfebrile temperature. These symptoms were first noticed three months before the examination and had become progressively worse. At the time of the examination the patient appeared very restless and nervous. He had marked "stare" but no exophthalmos. von Graefe's and Mobius's signs were absent. There was fine tremor of the hands. The skin was warm and moist. The thyroid gland was diffusely enlarged to moderate size, it was soft. There was no bruit or thrill over the thy-

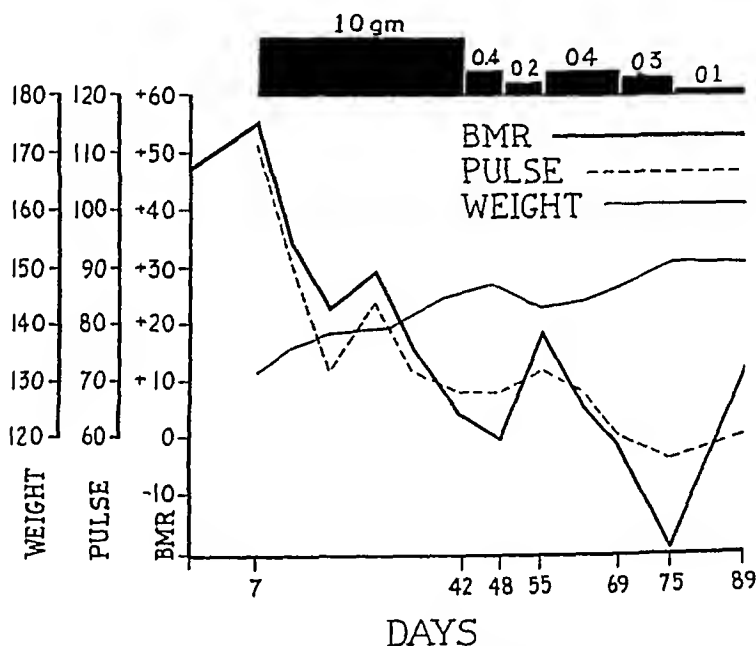


Fig. 108 (Case I) —The doses given in the chart are the total daily doses, which were administered in divided doses (See text)

roid. The pulse rate was 100 to 110, the blood pressure 140 systolic and 50 diastolic. The basal metabolic rate was +50. The response to thyroacil therapy (0.2 gm were administered five times daily) was prompt. The basal metabolic rate, the basal pulse rate and the weight are charted in Figure 108. Clinical manifestations improved accordingly.

Maintenance treatment with such small doses is continued for several months. The question whether administration of the drug can eventually be discontinued is under study. Astwood<sup>17</sup> has reported several patients who after having been maintained for many months on small doses continued to be in perfect health for several more months after discontinuing treatment. A trial at discontinuing seems

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Does the use of thiouracil instead of iodine in preoperative management of thyrotoxic patients offer any practical advantage? There are, of course, patients who do not tolerate iodine, and for such patients the possibility of an alternative is gratifying. Then there are those mis-handled by too prolonged administration of iodine who can be adequately prepared with thiouracil. For the ordinary case, neither intolerant nor irresponsive to iodine, an advantage has been seen in the fact that with the use of thiouracil the thyroid function can be decreased to the desired normal or even hypothyroid level. In contradistinction the basal metabolic rate in moderately severe or severe cases of thyrotoxicosis cannot as a rule be reduced to entirely normal levels with iodine and patients have to be operated upon in a more or less mild thyrotoxic condition. Evidently the operative and postoperative course will be smoother and less fraught with danger if thyroid function has been depressed to lower levels with thiouracil. On the other side of the balance sheet are two facts, one the possibility of drug sensitivity and consequent toxic manifestations and, secondly, increased vascularity of the gland. This latter fact may tend to increase technical difficulties of the operation. Some surgeons have stressed this fact but in our own experience, or rather in that of our surgical collaborators, it is negligible and far outweighed by the greater safety due to the better condition in which the patient is brought to operation.

Bartels<sup>18</sup> has given iodine after thiouracil has exerted its desired effect thereby attempting to operate on an involuted goiter. We have no personal experience with this procedure but have some doubts as to the physiologic rationale. As long as the thiouracil effect lasts entrance of iodine into the thyroid gland will be blocked. If thiouracil is withdrawn iodine will enter the gland to the extent to which the thiouracil effect is waning. The purpose for which thiouracil was given may be defeated by such a procedure.

All this is still in the investigational stage and further experience only will tell whether or not thiouracil will replace iodine in the routine preoperative treatment of thyrotoxicosis. At present we can already see a definite place for it in cases in which iodine is either not tolerated or ineffective, and in very severe cases in which, in all probability, improvement with iodine beyond definitely toxic though milder levels will not be attained.

#### COMPLICATIONS

The knowledge and careful record of complications accompanying therapy is particularly important in the case of a new drug the use of which is in the investigational stage. The following are possible complications attending thiouracil therapy.

- 1 The occurrence of myxedema in the course of treatment was mentioned on page 1365. It is a harmless complication and signs and symp-

# DYSMENORRHEA

EDWARD H. BISHOP, M.D.\*

DYSMENORRHEA is one of the most common of all gynecologic complaints and is experienced to some degree by at least 50 per cent of all women. In spite of its frequency it still remains one of the most difficult problems to treat satisfactorily. The greatest complicating factor is that dysmenorrhea is a symptom and, unfortunately, is a symptom of not one but many varying pathologic conditions. In order to treat this symptom with any degree of success the etiology must first be determined and the problem approached in a logical manner. Too often dysmenorrhea is treated as a disease entity and too often it is treated on an empirical basis. Since this only too frequently results in failure, dysmenorrhea is often relegated to that group of discomforts which must be tolerated rather than relieved. Therefore it seems best to discuss the management by first considering the various types and causes. In this way one may develop a rational and logical consideration of the treatment.

## DIAGNOSIS

Dysmenorrhea may be divided into primary and secondary types. When some demonstrable pelvic disturbance is present with dysmenorrhea as a symptom, it is classified as *secondary* dysmenorrhea. When no abnormality can be detected in the genitalia to account for the pain it is known as *primary* or *functional* dysmenorrhea. Since secondary dysmenorrhea is usually easier to diagnose and easier to treat it seems best to search for any of the possible causes for this type as the first step in the management of this problem.

The initial procedure undertaken in order to determine the etiology is a careful history and complete physical examination. In addition to the usual gynecologic history the physician should obtain a detailed history of the menstrual pain, the age at which it first occurred, the time relationship to the menstrual period, the location and radiation of the pain and recent changes in the intensity of the pain. These details often serve as valuable clues to the final diagnosis. As examples, the menstrual cramps which are primary in type usually first occur early in life, do not increase with age and occur in the early part of the menstrual period; the dysmenorrhea associated with endo-

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From the Department of Gynecology, Jefferson Medical College, and the Pennsylvania Hospital, Philadelphia.

\* Instructor in Gynecology, Jefferson Medical College; Clinical Assistant in Gynecology and Obstetrics, Pennsylvania Hospital; Assistant in Gynecology and Obstetrics, Methodist Hospital.

Some patients responding well initially to iodine medication become increasingly worse under prolonged treatment. The interpretation of such an event is controversial. Whether the patients become refractory to iodine, or whether their thyrotoxicosis progresses in its natural course in spite of some incomplete repression by iodine is not so important from a clinical standpoint. Some mild cases of thyrotoxicosis may in fact be permanently relieved by iodine medication. Mild cases only should be subjected to such an attempt, and even amongst them selection should be made on the basis of careful study.

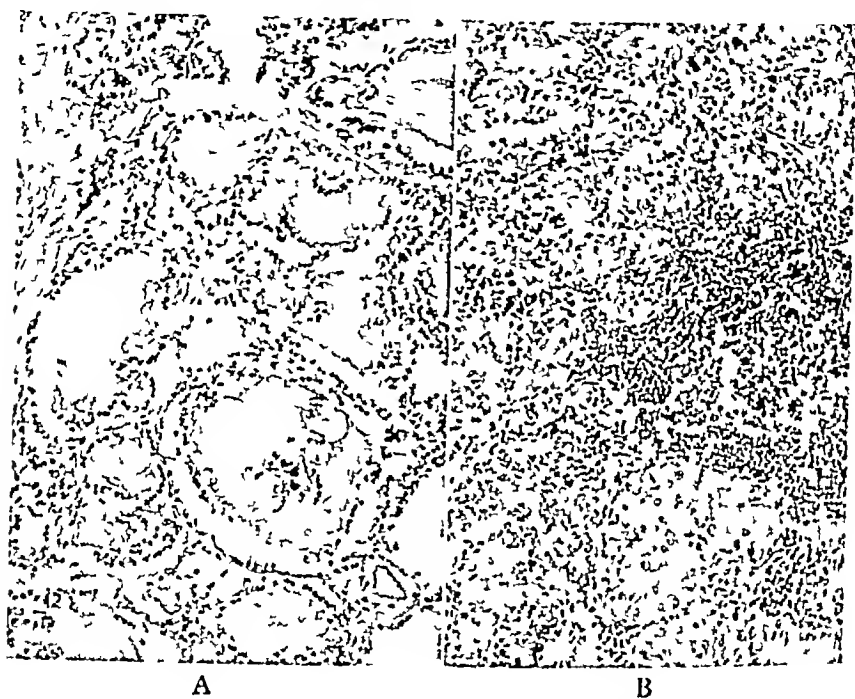


Fig. 111 (Case II) —Section of thyroid gland obtained at autopsy (Magnification  $\times 135$ . Fixation with Zenker formalin-hematoxylin-eosin stain) A, Involution (iodine effect) in small areas B, Hyperplasia, lymphocytic infiltration. This picture is prevalent in this case showing lack of iodine effect in spite of three months' treatment with Lugol's solution.

Unfortunately it has become a habit in medical office practice to give iodine over long periods of time. The patient is frequently then referred for surgery or for medical treatment with weight loss, tachycardia or auricular fibrillation, and high basal metabolic rate. The fact that he is not responding to further iodine medication poses a serious problem. Thiouracil offers a means to prepare such a patient satisfactorily for operation, or to treat him medically, as the case may indicate. A peculiar feature of several such cases in our observation was that metabolic response preceded a decrease of heart rate by several weeks.

the pendulum of opinion away from the mechanical theories many of these milder cases of endocervicitis with stricture are overlooked. Supplementing the dilatation of the cervical canal, treatment should be directed toward other evidences of endocervicitis such as eversion, nabothian cysts and ectropion. Cauterization or coagulation offers the best method of treatment and if done lightly and carefully one does not need fear further stricture as a result.

In a small group of cases it has been found that ureteral strictures or ureteral abnormalities may be the cause of the pain at the time of the menstrual period. In any case in which urinary symptoms are present a complete urologic investigation is indicated.

Among the laboratory procedures which are sometimes helpful are determination of the red cell count, hemoglobin and basal metabolism. Mild anemia and hypothyroidism are not prominent among the causes of secondary dysmenorrhea but may often be contributing factors.

#### TREATMENT OF PRIMARY DYSMENORRHEA

After one has searched for and removed the causes of secondary dysmenorrhea, there still remains the very large group of cases in which one can find no physical basis for the symptoms—the so-called primary or functional type of dysmenorrhea. Many theories have been advanced to explain the pain experienced by this group of patients, but without agreement. As yet no offered concept fits all cases and, therefore, they must be treated on a more or less empirical basis. Undoubtedly there is a large psychic element present in all of these cases which results in a marked lowering of the pain threshold. Nevertheless, these patients cannot be dismissed as “neurotic” but instead one must find some method of relieving their pain. It seems best to treat these patients in the following order.

1. **General Measures.**—Good physical and mental hygiene should not be forgotten as part of our therapeutic armamentarium. Clow has reported that she was able to reduce the incidence of dysmenorrhea in a girls' school 70 per cent by having the girls take warm showers and moderate exercise during their menstrual periods, by using laxatives as indicated and by placing them on a proper, well balanced diet.

The nature of the complaint should be explained to the patient in detail. She must be made to realize that menstruation is a normal function and that normal activities should be maintained during this time. The patient who anticipates a debilitating period and prepares for it by incapacitating herself before the actual pain appears usually fulfills her anticipations.

2. **Analgesics, Antispasmodics and Heat.**—The use of one of the many analgesics (acetylsalicylic acid, phenacetin, and so forth) and light sedation still remain as the most satisfactory method of treatment for the milder cases. The various antispasmodics (including the synthetic



CASE III—E. C is a white woman aged forty-five years Eighteen years ago a thyroidectomy was performed because of exophthalmic goiter The patient was well after that but her exophthalmos remained unchanged For the past two years she has had considerable worries and emotional upsets She became increasingly more nervous She had palpitations and lost some weight in spite of good appetite On examination exophthalmos of considerable degree, with positive von Graefe's and Mobius's signs, was noted The skin was moist and warm There was no tremor The pulse rate was 120, the blood pressure 140 systolic and 90 diastolic The basal metabolic rate was +23

This patient evidently had mild recurrent thyrotoxicosis She wished to avoid an operation if possible Thiouracil (0.2 gm) was given five times daily for one week At the end of this period she felt greatly improved and much less nervous The pulse rate was 96, the basal metabolic rate +9 Thiouracil dose was reduced to 0.8 gm. (0.2 gm given four times daily) The following day the patient felt sick, ached all over and her temperature rose to 99.6° F Medication was stopped. One day later a maculopapular rash appeared Three days later she had recovered entirely and took two doses of thiouracil, 0.2 gm each, at two-hour intervals Several hours after the second dose she had a chill, fever and became jaundiced The drug was discontinued Two and a half weeks later she was seen again Her basal metabolic rate was +34 She was very nervous and complained of palpitations Operation was strongly advised but the patient insisted on trying the drug once more, because of the improvement she had originally experienced, in spite of the fact that she was warned that toxic reactions would almost certainly follow She took 0.2 gm, chill and fever following one hour later About twelve hours after taking the drug she was jaundiced The serum bilirubin was 2.9 mg per 100 cc., the direct van den Bergh reaction positive Dye excretion test revealed 60 per cent dye retention A fine maculopapular rash was present Fever receded the following day and the jaundice and rash cleared up within two days (serum bilirubin 0.6 mg per 100 cc)

Another patient reacted in an almost identical manner, the first symptoms appearing on the ninth day of treatment and toxic responses being elicited with increasingly smaller doses

In a third case of our observation thiouracil was well tolerated for a period of eight months The patient then acquired an acute upper respiratory tract infection with fever Thiouracil was continued during this period A maculopapular rash and leukopenia followed Two days after treatment was discontinued the rash had disappeared and the leukocyte count had returned to normal Attempts to reinstitute treatment, however, were immediately followed by a drop of leukocytes on two occasions The rash did not reappear It seems possible that in this case the mild infection had sensitized the patient to thiouracil Be that as it may, further treatment with this drug appeared impossible

The not infrequent occurrence of "toxic" manifestations is the most important reason to restrict the use of this drug for the time being to institutions engaged in investigation The nature of the toxic phenomena is not clear, and there is so far no proof, but some circumstantial evidence, that these phenomena are due to sensitization to the

ate, estriol glucuronides, ethinyl estradiol, estrone and estradiol benzoate may be used in comparative dosages large enough to inhibit ovulation. Nevertheless stilbestrol is the drug of choice because of its comparative low cost, its effectiveness and the simplicity of its administration. The natural estrogens may be used when the toxic effects, such as gastrointestinal disturbances, prevent the use of stilbestrol.

The use of testosterone propionate is based on the same concept as the use of the estrogenic substances, namely the inhibition of the gonadotropic factor of the pituitary with the subsequent suppression of ovulation followed by an anovulatory menstrual period which is usually free of pain. This drug is not as safe as the estrogens because the therapeutic dose may approach the dose which results in masculinizing changes.

The endocrine treatment of dysmenorrhea should be undertaken with the greatest of caution. It should be employed only in selected cases and then only for short periods of time. Even though we may relieve the patient symptomatically, the cure is only temporary and as yet we do not know the late effects on the endocrine system due to the administration of these products over long periods of time. We may permanently interfere with ovulation or at the least seriously disturb the delicate endocrine balance. As long as this is a possibility it does not seem justifiable to use this method of treatment until all other forms have been exhausted.

4. **Exercise.**—Adams, and more recently Billig, have proposed the thesis that dysmenorrhea may be caused by a postural defect resulting in contracted ligamentous bands of the pelvic fascia. Billig states that at the time of menstruation, due to the action of the ovarian hormones, there is a further shortening of these bands resulting in an irritation of the spinal nerves passing through and by them. He has devised some simple exercises which result in a gradual lengthening of the ligaments involved, thus freeing the nerves from their impingement. The results published by Billig and others have been quite encouraging. Recently Haman has corroborated these findings and suggested a modification and simplification of the exercises devised by Billig.

5. **Hypnosis.**—Hypnosis has been used satisfactorily in a small series of cases but the field of its usefulness is limited by the necessary selection of cases and the scarcity of competent and interested psychiatrists. The results are probably due to a raising of the pain threshold by posthypnotic suggestion.

6. **Neurological Treatment.**—After all of the above methods of treatment have been used there still remains a group of patients who have intractable and incapacitating pain at the time of the menses. For these, the only remaining treatment is surgical, by the performance of a resection of the superior hypogastric plexus or the presacral nerve. The results of this operation are quite satisfactory when the cases have

metabolic rate of +36 The patient was given thiouracil, 1 gm daily, the dose being reduced after a full effect was achieved, and is now maintained in an apparently normal state with 0.2 gm daily

Obviously medical treatment of thyrotoxicosis with thiouracil is limited to the diffuse toxic goiter, the primary thyrotoxicosis The secondary thyrotoxicosis of the toxic nodular goiter or toxic adenoma of the thyroid poses entirely different problems Suppression of "toxicity" in this type is not enough The large nodular goiter is an object of surgery because of the mechanical mischief it produces by encroaching on the trachea, and because of the possibility of malignant degeneration Whether or not the stimulation of hypertrophy and hyperplasia induced by thiouracil could precipitate malignant growth in such a nodular goiter is at this time a matter of speculation But unquestionably the enlargement of the goiter not infrequently encountered during prolonged administration of thiouracil would tend to aggravate signs of pressure on neighboring organs A comparatively short preoperative course of thiouracil medication does not meet these objections raised for the medical "permanent" treatment of nodular toxic goiter

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## THE MENOPAUSE

JOHN B. MONTGOMERY, M.D., F.A.C.S.\*

THE word "menopause" literally refers to cessation of the menstrual function. However, it is commonly used interchangeably with the broader term "climacteric" which denotes that transitional period in the life of woman characterized by ovarian failure, loss of the child-bearing function, cessation of the menses and regressive changes in the genitalia.

Menstruation usually ceases between the ages of 40 and 50, the average being about 47. When the menopause occurs earlier it is usually due to surgical removal of the ovaries, radiation therapy, prolonged lactation or some endocrine disturbance which is associated with a lack of ovarian function. However, in occasional instances which are often influenced by heredity, the menopause may occur spontaneously at an early age. In about 10 per cent of women menstruation does not cease until after the fiftieth year and occasionally the menopause is delayed until 55. Although normal menstruation has occasionally been noted beyond this age, such an occurrence should always be investigated by diagnostic curettage and cervical biopsy to rule out uterine malignancy or an ovarian tumor, even though the cycles are reported to be normal.

The menopause is an integral part of the process of aging; in no sense can it be regarded as a disease. However, the profound changes that occur in physiologic processes and in physical structure, together with associated emotional and nervous disturbances sometimes are responsible for annoying symptoms. On the other hand these changes, together with the freedom from menstrual distress and from fear of pregnancy at times result in marked improvement of general health, increased vitality, and a sense of well-being beyond anything that the individual has experienced during her active menstrual life.

### ETIOLOGY

**Endocrine Changes.**—The underlying cause of the menopause and its associated phenomena is failure of ovarian function with its related endocrine disturbances. This is apparently due to the normal aging of the ovary which causes it to become refractive to the gonadotropic hormone of the anterior pituitary. Failure of ovulation is probably the

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From the Department of Gynecology, Jefferson Medical College, Philadelphia.

\* Clinical Professor of Gynecology, Jefferson Medical College; Assistant Gynecologist, Jefferson Medical College Hospital; Assistant Attending Obstetrician, Bryn Mawr Hospital, Bryn Mawr, Pennsylvania.

# THE LEUKEMIAS

F R MILLER, M D \* AND D L TURNER, PH D †

A CONCISE definition of the leukemias is difficult because they comprise several diseases. They may best be defined as a group by several statements that apply individually and collectively to them. Sustained increases in the white blood cell count frequently occur in this group of diseases. The name "leukemia" was derived from the pale color of the blood occasioned by such increases in white blood cell counts, however, all leukemias are disorders of the blood-forming organs rather than of the peripheral blood, so that leukopenic or normal white blood cell counts are compatible with the term leukemia. The presence of abnormal cells in the blood is of greater importance than the level of the leukocyte count.

## THEORIES OF ORIGIN

Three theories pertaining to the origin of these diseases have been advanced. One of these is that they are caused by infection, another is that they are neoplastic growths and the third is that they are brought about by disordered hormonal control or metabolic imbalance.

**Infective Theory**—The first cases were described nearly one hundred years ago by Craigie, later by Bennett and Virchow. In the past forty years, many investigators have tried to prove that these diseases were brought about by infective agents. The literature contains many reports of attempts to culture bacteria from the nasal passages, mouths, throats, blood streams, stools, and urine of patients with these diseases, and animal passage of organisms from these sources has been tried frequently. Experiments of this type have not yielded consistent results nor have they accomplished the reproduction of any of the leukemias in other animals. Only one series of experiments is at all pertinent in this regard and that is the work started by Ellerman<sup>1</sup> on fowl leukemias. An agent that will pass a porcelain filter candle is causative of the disease in these animals. This work has not been duplicated in experiments with human leukemia, so that there seems little evidence that human leukemia in any of its forms is caused by either bacterial or filter-passing organisms.

**Neoplastic Theory**—A vast amount of work has been reported on mammalian leukemia. Much of this has been concerned with leukemia

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From the Charlotte Drake Cardeza Foundation, Jefferson Medical College, Philadelphia

\* Associate Professor of Medicine and Assistant Director, Division of Hematology, Jefferson Medical College, Philadelphia

† Research Chemist, Jefferson Medical College

that are alarming to the patient, frequently creates a marked state of anxiety. This in itself may be responsible for many of the most distressing symptoms. These influences are likely to be especially damaging to the woman with marked psychoneurotic tendencies. On the other hand, although the symptoms of organic mental disease may be precipitated at the time of the menopause there is no evidence to indicate that psychoses are actually produced by failure of ovarian function.

**Physical Changes.**—General physical changes are usually emphasized by the tendency to gain weight and particularly by the deposit of fat over the hips and girdle region. In some women these changes result in refinement of contour and increase in appearance of general good health which enhances their physical attractiveness. Regressive changes in the genital system begin after the estrogenic influence wanes. The endometrium becomes thin, the uterus becomes small and firm due to the atrophy of the myometrium and the development of fibrous tissue. The vaginal mucosa decreases in thickness (atrophic vaginitis, senile vaginitis) and the underlying supportive tissues undergo atrophic changes that sometimes result in shortening and deformity of the canal. The cervix decreases in size and at times may be hidden from view because of contraction of the vaginal vault and adhesions of the vaginal mucosa. These changes also affect the endopelvic fascia so that inherent weaknesses are exaggerated and become manifest in the development of uterine prolapse, cystocele or rectocele. The external genitalia decrease in size. The mons becomes less prominent, the small labia shrink, the pubic hair becomes sparse and the mucous membrane becomes smooth and pale. Areas of leukoplakia are common and at times atrophic changes are extreme, resulting in kraurosis vulvae. In spite of these changes the vulvar glands may continue to secrete mucus, and sexual sensations and libido may be unimpaired. The atrophic changes in the genital system may also affect the urethra and neck of the bladder resulting in urinary frequency or stress incontinence. Atrophy of the breasts may be a prominent feature although this is sometimes disguised by deposition of fat.

#### SYMPTOMS

It is generally conceded that the great majority of women go through the menopause without symptoms which are severe enough to interfere with their general welfare. However, with the advent of hormone therapy and the free discussion of this problem in the lay press an increasing number of women are consulting their doctors for relief of symptoms which they attribute to the menopause. In dealing with this ever-enlarging group of patients it is well to remember that symptoms which are attributed to the menopause frequently may be due to underlying organic disease. Severe menopausal symptoms will be encountered in only about 10 per cent of the patients.

cific substance in the urine of patients with chronic lymphoid leukemia. We then presented evidence that the two specific substances were present in varying proportions in the urine of patients with acute and chronic myeloid leukemia, acute and chronic lymphoid leukemia, Hodgkin's disease, monocytic leukemia and lymphosarcoma.<sup>6</sup> In this work, we showed that the two substances occurred in the acid fraction of hydrolyzed urine extract, that one could be separated from the other, and that the myeloid substance was a keto-acid and the lymphoid substance a hydroxy-acid. It was further demonstrated that the myeloid substance could be converted to lymphoid substance by reduction, and that the lymphoid substance could be changed to myeloid substance by oxidation. From these experiments the two substances seem to be closely related chemically.

In the bio-assay of the extracts and fractions of extracts guinea pigs were used. At first each animal received the extract from approximately 10 liters of urine, and this was given in divided doses. In later experiments the extract from 4 to 5 liters of urine was given to each animal and when two or more fractions were made from an extract proportionate doses were given. In these later experiments, the fractions were often oily and insoluble in water, and were given in olive oil or undiluted. Such fractions were given in not more than five doses and at four to five-day intervals.<sup>7</sup>

In the animals that have received these extracts or fractions of them, we have been able to recognize three main pathologic pictures. These we term myeloid reactions, lymphoid reactions, and the reactions of Hodgkin's disease.

*Myeloid Reaction*—The myeloid reaction occurs in animals that have been given extracts of the urine of patients with acute or chronic myeloid leukemia and the noncarbinol fraction separated from the extracts of urine of patients with acute and chronic myeloid leukemia, chronic lymphoid leukemia, monocytic leukemia and Hodgkin's disease. This reaction also has been found after the use of material obtained by the oxidation of hydroxy-acid fractions. After oxidation, the myeloid reaction appears in animals given the fraction containing non-carbinol acids. This myeloid reaction consists of hyperplasia of the myeloid elements in the bone marrow, frequently enlargement of the spleen with more or less myeloid metaplasia being in evidence and enlargement of the liver, in which there is myeloid infiltration or metaplasia in the periportal spaces as well as in between the liver cords. The metaplasia of cells includes the development of erythroid, leukoplasmic and platelet-forming elements. The adrenals are almost invariably enlarged, and under the capsules in the cortex, and at times in the medulla, new formation of myeloid elements is discernible.

*Lymphoid Reaction*—The lymphoid reaction occurs in animals that have been given the extracts of the urine from patients with chronic lymphoid leukemia, acute lymphoid leukemia and lymphosarcoma, as

## DIAGNOSIS

In dealing with the menopausal woman, a thorough survey of the patient is absolutely essential before her symptoms can be evaluated and a sound rational plan of treatment can be outlined. The problems of differential diagnosis presented by the multiplicity of symptoms are often very complex and may tax the ability of the most experienced physician. One is never justified in assuming that the symptoms are functional in origin. A complete history and a complete physical examination are essential. This should include careful examination of the breasts, bimanual examination of the pelvis, inspection of the vagina and cervix through a speculum, digital palpation and proctoscopic examination of the rectum. A blood count and urinalysis should always be made. Basal metabolism determination, electrocardiogram, eye-ground study, blood chemistry, gastrointestinal x-ray and the like should be carried out promptly if suggestive symptoms are present. Such a thorough study is really an important part of treatment. It will go far toward allaying the patient's anxiety and increasing her confidence in the opinions and advice of her doctor.

## TREATMENT

In treating the menopausal patient, the physician must be ever conscious of the fact that the physiologic disturbances that produce the characteristic symptoms and physical alterations are due to the normal process of aging, and therefore cannot be prevented or reversed. It is important also to recognize the influence of the patient's nervous temperament, emotional instability, and her anxiety which is so often secondary to fears which arise from a lack of understanding of the true significance of the menopause.

Treatment should always begin with a simple, brief explanation of the phenomena underlying the menopause and of their significance. The patient should clearly understand that she is in no unusual danger of serious physical or mental illness. She should realize that rather than a portent of imminent old age, the menopause is nature's way of freeing her from the annoyances of menstruation and the hazards of pregnancy and childbirth at an age when she can live for many more years in the vigor of good health. A few minutes spent in simple explanation plus the assurance that results from a careful complete physical examination goes a long way toward alleviating the anxiety that underlies many of the menopausal symptoms. In many cases no further treatment is necessary.

**General Measures.**—In most instances, general medical measures should be tried before instituting endocrine therapy. Measures to improve the general hygiene of living are very helpful. Many women suffer from overwork and lack of sleep. The cares of family life are heavy upon them. Faulty diet, with excesses of coffee and cigarettes, are not uncommon. Constipation, anemia and obesity are frequent.



and Hodgkin's disease, or from the lipoidal fraction of normal beef liver. One of these is an hydroxy-acid, the other a noncarbinol acid. They are interconvertible by oxidation and reduction and their activity changes as their chemical nature is changed by such reactions.

Because of this work, we have postulated the following theory to account in part for the physiologic activity of these two substances. We believe that these two substances regulate normal hematopoiesis.

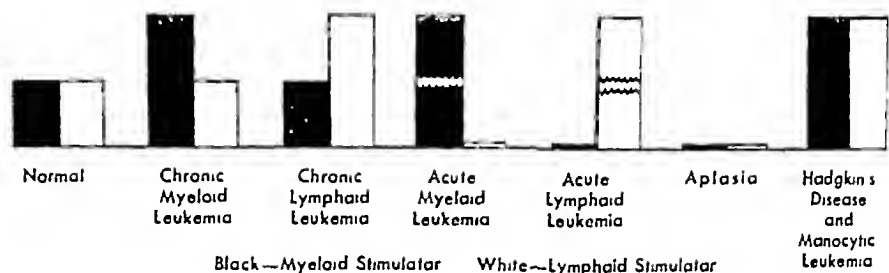


Fig 112—Theoretical occurrence of stimulating substances in the normal individual and in several of the blood dyscrasias

The first chart (Fig 112) shows in a rough way what we assume to be the proportions of these substances in normal tissues and body fluids and in the tissues and body fluids in several of the blood dyscrasias. The second chart (Fig 113) is based on the distribution of these two substances as we have found them in the urines of normal individuals and individuals with several of the blood dyscrasias.

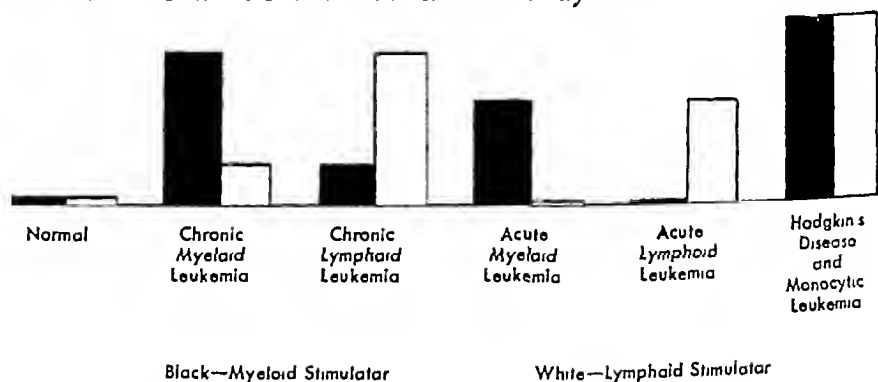


Fig 113—Distribution of stimulating substances in the urines of normal individuals and those of several of the blood dyscrasias

The differences in the charts may be explained by the fact that the absence of substances is more difficult to demonstrate than their presence, but even though we were unable to find either substance in the normal human urine we have demonstrated the occurrence of both substances in the lipids of normal beef liver.

*Mode of Action of Myeloid and Lymphoid Substances*—We suggest that these substances are mutually reciprocal in action. The myeloid substance stimulates myelopoiesis, i.e., proliferation without maturation.

treatment may possibly delay the climacteric and simply "put off the evil day." Speaking of intensive estrogen therapy, Hamblen states that "the entire orderly process of sexual aging may be frustrated and unless therapy is discontinued the climacteric indefinitely may be postponed."

It is well known that estrogen therapy frequently results in uterine bleeding. Although such an occurrence usually is due to overdosage, it is always alarming to the patient. If the bleeding is scant and of short duration, endometrial curettage may be deferred provided careful pelvic examination reveals no abnormalities. However, if there is any recurrence of bleeding, diagnostic curettage should be done immediately and the curettings examined by a competent pathologist to rule out carcinoma.

**INDICATIONS FOR ESTROGEN THERAPY.**—Only a small percentage (10 to 20 per cent) of menopausal women require estrogen therapy. The outstanding indication is severe vasomotor symptoms (flushes, sweats, chills) that have not responded to general medical measures. It may be tried as a therapeutic test for relief of severe headache after careful examination has ruled out organic disease and other methods of treatment have failed. Such a trial may be of value also in some patients with painful joints (knees, shoulders). Its value in vaginitis secondary to atrophic changes in the mucosa is well recognized but in this instance local application is preferable. Many clinicians believe that hypertension which originates during the climacteric may be benefited by estrogen therapy. Its use is probably justified in the management of these cases but the administration, as already pointed out, may have harmful effects.

It is questionable whether estrogens should ever be given to relieve menopausal symptoms in patients who are experiencing the irregular uterine bleeding that is so common during this period. Such bleeding is most likely to occur during the early stages of ovarian failure and is often associated with excessive estrogen levels (polyfolliculin phase). If facilities are available, determination of the output of estrogenic hormones in the urine or a study of vaginal smears will settle this point. The first of these procedures requires a laboratory and special equipment to make hormone assays. The second has recently been simplified by Shorr who has developed a technic which can be acquired readily by one trained in routine clinical laboratory procedures. It is based upon Papanicolaou's studies which showed that the estrogen deficiency brings about "a vaginal smear pattern characterized by the absence of cornified epithelial cells, and the presence of many intermediate and small round and ovoid cells which originate from the deeper layers of epithelium plus many leukocytes." Variations in the smear pattern indicate various degrees of estrogenic deficiency. Although these studies are helpful in determining the need for estrogenic therapy, they are by no means essential for the intelligent clinical management of these patients. Careful evaluation of symptoms with special consideration of

to benzol or its derivatives, the use of arsenical or sulfonamide drugs, infection of various types including pneumonia, tuberculosis and syphilis, as well as many other related and unrelated factors or agents, have been observed as the point from which the change toward the leukemic process occurred. Each cannot be the cause of leukemia, but each can act to change normal hormonal control of blood formation so that leukemia results. We believe that these incidents and agents are the factors that upset the balance of normal hematopoiesis.

### DIAGNOSIS

The diagnosis of the leukemias rests on knowledge of their clinical manifestations as well as on certain well-established laboratory data. In those cases of chronic myeloid leukemia in which the spleen is enlarged, there is tenderness of the sternum, the leukocyte count is elevated and there are numerous myelocytes in the peripheral blood, the diagnosis presents no special problem. Nor is the diagnosis of most cases of chronic lymphoid leukemia at all difficult, because in these patients certain of the lymph nodes are usually enlarged, the spleen may or may not be enlarged and the majority of the white blood cells will be lymphocytic.

The greatest difficulties in diagnosis are encountered in the acute leukemias, although any one of the leukemia group may present a problem if the leukocyte count is leukopenic or normal. Many acute leukemias show a preponderance of primitive or blast cells. It is frequently difficult to decide whether these are lymphoid, myeloid or monocytic. A good peroxidase stain of a sample of the peripheral blood will be of value, because the lymphoid cells are never peroxidase-positive. A positive reaction will orient the cells as either monocytic or myeloid. Fortunately, in many of the acute myeloid leukemias, sufficient differentiation of the cells has occurred so that they will be easily recognized as early myelocytes. If the cells are of the monocytic strain they may or may not be peroxidase-positive, however, when they are positive, the granulation is much more dust-like than the granulation of the myeloid cells.

Anemia is an outstanding feature of all acute leukemias, but early in acute lymphoid leukemia this is not as marked as it is in the early phases of acute myeloid or acute monocytic leukemia. Purpura and hemorrhagic tendencies are present in all acute leukemias and are most marked in the acute myeloid type. Platelet counts are frequently low in all types. Lowered resistance is encountered in all acute leukemias, so that secondary infection is frequently seen. Infection and necrosis in the mouth is encountered more often in both acute myeloid and monocytic leukemia than in acute lymphoid leukemia. Ability to form antibodies seems to be lacking and the heterophile antibody test is invariably negative. In acute monocytic leukemia a sponginess and overgrowth of the gums is almost pathognomonic. Slight jaundice and

endocrine system in a state of imbalance. The best plan is to give the hormone for a short period of time, possibly for two or three weeks, and then stop for a week and repeat. These cycles of therapy should not be continued for more than two or three months and usually should be stopped much sooner. If severe symptoms recur the treatment may be repeated for one or two cycles. The objective should be to control the symptoms promptly, using large initial doses if necessary and then reducing the dose and the length of the cycles so that the smallest amount that will relieve the symptoms is given. Under no circumstances should the administration of estrogens be continued indefinitely.

Oral administration is highly satisfactory and is the method of choice in most patients. The initial dose should be small, 0.25 mg. of diethylstilbestrol or 1 mg. of estrone sulfate daily. This can be varied from time to time until the optimum dose is found. The untoward effects of oral therapy can be prevented in most instances by using small doses and shortening the period of administration.

Intramuscular injection should be limited to patients in whom relatively large doses are necessary to control severe symptoms quickly. Ten thousand international units of an estrone preparation or 2000 rat units of an estradiol preparation given every four days for three to six doses are usually sufficient. Occasionally larger initial doses are necessary but these should be discontinued as soon as possible in favor of oral therapy.

The vaginal administration in the form of suppositories is indicated when there is an associated senile vaginitis. Cyclic administration of 2000 international units every third day for six doses is usually sufficient.

The subcutaneous implantation of pellets or crystals of estrogenic substances has been used very satisfactorily. It may be of distinct value in occasional instances where administration of the hormone is needed over a long period of time. Such an instance may occur following surgical castration in a young woman.

**X-ray Therapy.**—Attempts to depress the anterior pituitary have been reported with varying results. The danger of injury to the pituitary and adjacent tissues makes its use hazardous. It is not recommended.

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now favor the use of small scattered doses of "spray" irradiation rather than heavy doses over one area<sup>9</sup> The white blood count may not be reduced as rapidly, but if such patients are treated once a week with 10 to 20 r units, the disease may be controlled with fewer major relapses The effects of this type of therapy resemble those obtained with radio-active phosphorus

*Radio-active phosphorus* may be employed by giving two or three injections of 25 millicuries in a six-week period In many cases this amount will be sufficient to cause remission, lowered white blood cell count, and reduction in spleen size as well as reduction in bone marrow activity for six months to one and one half years It must be remembered that the effect is that of irradiation and in the end the result will be the same as in those cases treated with other types of irradiation It has a definite advantage in that the material almost never causes radiation sickness Radio-active phosphorus may be given again as the disease progresses, but it is rather ineffectual if the patient has previously received much x-ray irradiation At present the use of this material is limited because of the war which limits manufacture of it

We have found that the alternate use of x-ray and *arsenic* is of some value Some patients will react well to Fowler's solution after they seem to have had as much irradiation as they will tolerate We do not agree with Forkner<sup>10</sup> that patients can be maintained for long periods of time on Fowler's solution, but disagreement is perhaps academic in that we believe they could be maintained well for long periods of time if they could tolerate its use Arsenic can damage the liver, the skin, and the intestinal tract as it brings the hematopoietic system into control Because of these untoward changes we feel that it is best to give no more than 7 minims three times a day, and at the onset of signs of intoxication, to discontinue the drug for four weeks to two months, after which it can be reemployed With this drug it is always best to start with small doses and gradually build up to the larger ones We have found that patients taking Fowler's solution tolerate it better if they are given large amounts of vitamin C

**Chronic Lymphoid Leukemia**—Treatment of chronic lymphoid leukemia depends to a certain extent on the amount of lymph nodes involvement as well as the level of the leukocyte count There are a number of patients with chronic lymphoid leukemia who have relatively little lymph node enlargement and whose white blood cell levels are usually under 50,000 In these cases there is usually no anemia Such patients should not be given irradiation therapy until it is apparent that the lymph nodes are increasing in size and the leukocyte count is increasing They should, however, be given large doses of *brewers' yeast*, i.e., 3 to 30 gm a day This seems to tend to maintain them at lower leukocyte levels and also to retard to a certain extent the growth in size of the lymph nodes

If lymph nodes are enlarged and there is evidence of bone marrow involvement, x-ray irradiation should be given *Transfusions* should be

form. Although these forms are available upon request\* they are not essential. Physicians may draw their own forms upon ordinary graph paper. Grids with five lines to the inch are most satisfactory, and if  $\frac{1}{8}$  inch is allowed horizontally for each day, and  $\frac{1}{8}$  inch vertically for each  $\frac{1}{8}$  degree Fahrenheit the resultant graph will be well proportioned. The patient is instructed to take her temperature rectally with an ordinary clinical Fahrenheit thermometer for five minutes each morning upon awakening, before rising, drinking, eating or smoking. Some investigators secure evening (bedtime) readings, and some have

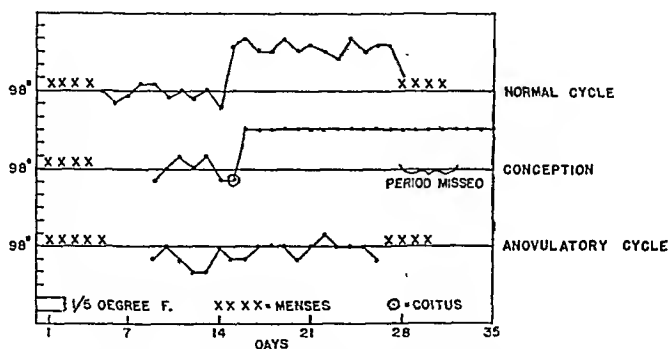


Fig. 180.—The first graph (*top*) shows the temperature curve during a normal menstrual cycle. During the first portion of the month the level is relatively low, it rises abruptly after a slight drop about fourteen days before menstruation and remains elevated until the next menstrual period. Then it drops and the entire cycle is repeated. The second graph was plotted by a patient with normal twenty-eight day cycles. On the fifteenth postmenstrual day her husband, who had been away at an Army Camp, came home “on a twenty-four hour pass.” The following day the temperature rose, the patient conceived, and the high temperature level was maintained until after the period was due. If the high temperature level is maintained for more than sixteen days, in the absence of organic causes for fever, it is probable that the patient is pregnant. Hence the temperature graph is of some use in diagnosing pregnancy, and for this reason has been called “the poor man’s Friedman test.” The third graph was drawn by a woman of 43 whose menstrual intervals varied from month to month. Some cycles showed the typical curve of the first graph and it was assumed that ovulation had occurred. In the flat graph shown above it is presumed that ovulation did not occur. In this particular case the assumption was not confirmed by endometrial biopsy. This has been done in other cases.

the temperature taken orally or vaginally. After comparing various methods I believe that the most consistent and clear-cut graphs are obtained from morning rectal readings.

If the patient exercises reasonable care, few errors will arise. Since the desired information is obtained from temperature variations and not from absolute temperatures the accuracy of the thermometer is of no great importance. Precision in reading the thermometer is important. Patients are instructed to note on the chart any obvious cause

\* Address requests to Ortho Pharmaceutical Corp., Linden, New Jersey.

## PITUITARY MYXEDEMA

CHARLES WILLIAM DUNN, M D, F A C P \*

THE term myxedema was introduced by Ord<sup>1</sup> in 1877 to describe an advanced state of hypothyroidism which he had observed in adults. In 1873 Gull<sup>2</sup> had described a corresponding clinical condition under the title "A Cretinoid Condition Supervening in Adult Life in Women." Myxedema was found by Ord to result from a fibroid atrophy of the thyroid, there was great diminution in size and weight of the thyroid and histologically the gland showed disappearance of the acini and colloid. Later myxedema has been found to result from syphilitic and actinomycotic inflammation of the thyroid, Riedel's ligneous thyroiditis, it has sometimes been observed after exophthalmic goiter,<sup>13</sup> thyroidectomy, x-ray therapy of the thyroid, post-thyroidectomy iodine therapy and acromegaly.

Humphrey Rolleston\* called attention to the possibility that "destruction of the pituitary and the resulting absence of thyrotropic hormone might be expected to cause myxedema" and referred to a man with symptoms of myxedema and feminism who was found to have an enormous hemangioma of the pituitary and atrophy of the thyroid, adrenals and testes.<sup>4</sup>

Atkinson's<sup>5</sup> exhaustive study of 1319 reported cases of acromegaly revealed a high incidence of thyroid gland changes. He states that before Marie's report acromegaly was frequently erroneously diagnosed as myxedema because of the presence of the signs and symptoms of myxedema. In the 265 postmortem reports on acromegalia collected by Atkinson, notations on the state of the thyroid in 141 cases were normal, 23 cases or 16.3 per cent, atrophied, 10 cases or 7 per cent, cystic, 27 cases or 19 per cent, hypertrophied, 81 cases or 57 per cent. In the series of 1319 patients the physical examination of the thyroid was noted in 464 cases but only 9 cases of myxedema were reported. Of the above 464 patients, 86 or 18.5 per cent are recorded as having atrophied or small thyroids. In numerous cases in which the condition of the thyroid is not given, a record of improvement under thyroid therapy had been noted. Other cases are reported with symptoms which indicate that hypothyroidism existed, among these were bradycardia, total baldness, mental sluggishness and diminished muscular response to faradic stimulation. The subjective and objective signs and symptoms of hypothyroidism in one group of acromegalic cases in which notations of the state of the thyroid are given, the improvement observed following the administration of thyroid in another

\* Assistant Professor of Medicine, Graduate School of Medicine, University of Pennsylvania

Unexpectedly high or low readings are always suspect, and patients are instructed to shake down the thermometer and to repeat these readings before plotting them on the graph. An intrinsic error in the record arises through the fact that menstruation beginning after the patient has gone to sleep is usually not noted until the next day and hence may be recorded as beginning on the day after it actually commenced. Such an error adds one day to the apparent interval between the temperature shift and the next menstruation.

The critical reader may inquire whether there is any proof that the temperature shift is actually associated with ovulation. If he will for the moment regard the association as hypothetical, the graphs will be presented first and the question answered later.

The great body of evidence, derived from histologic examination of the endometrium and ovary, from hormone assays, from comparison with findings in the monkey, from searches for early human ova and from clinical experience point to the fact that, in the human, ovulation precedes menstruation by a fixed interval of about fourteen days. This belief is convincingly supported by Figure 181 which is made up of temperature graphs ranked according to the length of the menstrual cycle. It will be seen that the temperature shift always occurs in the neighborhood of fourteen days before menstruation, and that the interval between the temperature shift and the preceding menses varies in proportion to the total length of the menstrual cycle.

At this point a common mistake of clinicians may be pointed out. Since the normal cycle is twenty-eight days in length, and since ovulation occurs fourteen days before menstruation, it follows that in a twenty-eight day cycle ovulation occurs midway between periods. Misdirected by this fact, physicians often advise all their patients that ovulation takes place "midway between periods" and that intercourse at such a time is most likely to be fruitful. This is untrue, as reference to the graphs of the forty-five day cycle and the fifty-three day cycle in Figure 181 make quite clear. Patients should be told that ovulation occurs about fourteen days before menstruation and should be assisted in their efforts to calculate which day of the calendar month that will be.

If the patient has intercourse near the time of the temperature shift she will have a better chance of conception than if intercourse occurs only at other times in the cycle. The second graph in Figure 180 is an example of coitus accurately, though accidentally, synchronized with the temperature shift. Conception followed. Similar graphs are seen in Figure 183. Not only does intercourse at the time of the temperature shift offer the best chance of fertilization, but I have not yet seen a record followed by pregnancy unless intercourse took place at that time. Conversely, there are many records showing imperfect synchronization with no subsequent pregnancy; in these cases better timing was often successful.



of age in whom Dr F C Grant evacuated a pituitary cyst Following evacuation practically the entire cavity of the sella turcica was exposed The patient is now twenty-one years old and shows no signs of myxedema She has failed to mature sexually, has grown at a normal rate, but during the last year has gained considerable weight

The second patient was a man aged sixty-two years who collapsed at work and died within seventy-two hours Death was the result of an acute and therapeutically uncontrollable hypoglycemic state Autopsy revealed a large pituitary cyst in a greatly expanded sella turcica, only 10 per cent of the anterior pituitary lobe remained and microscopically this tissue was atrophic and of poor functioning quality The cystic

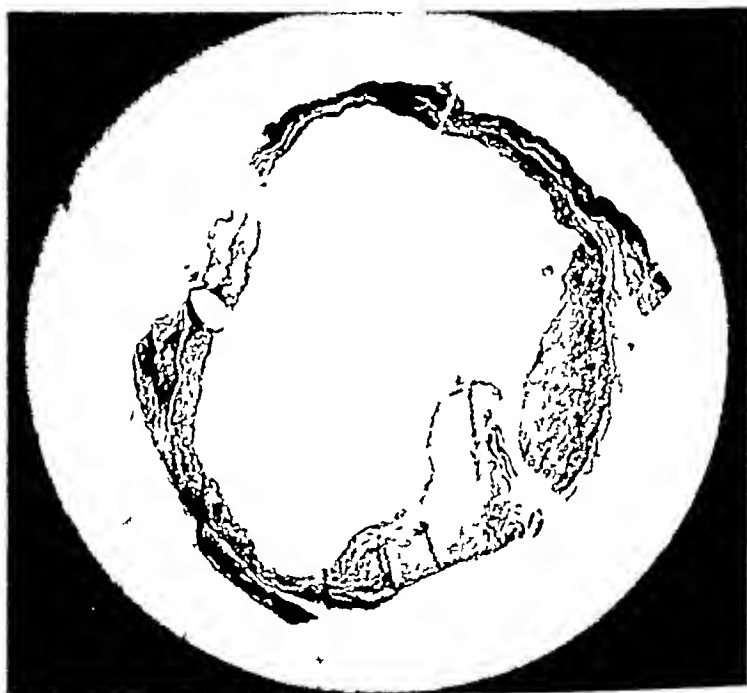


Fig 115 —Pituitary cyst in a male aged 62 Anterior pituitary cells were atrophic and degenerated Only 10 per cent of anterior lobe remained

degeneration had consumed the remainder of the anterior lobe (Fig 115) The sudden death apparently had been precipitated by an inflammatory process which appeared to originate in the posterior ethmoid region and extended basally to the diaphragma sella and involved the infundibulum This inflammatory reaction apparently shut off what little secretion had been produced by the remaining anterior pituitary tissue and a fatal collapse occurred The patient had been of normal health until five days prior to his death when he complained of dull recurrent headaches

Apparently maintenance of life is possible with but a fractional amount of anterior pituitary body These two cases indicate that as

spermatozoa by examining them under the ordinary microscope. In both cases one sees myriads of individuals agitated by an energy which appears purposeful. They move, to be sure, but of their age, their sex, their abilities we know little. In fairness to those who believe that motility is tantamount to potency, it must be admitted that bull semen

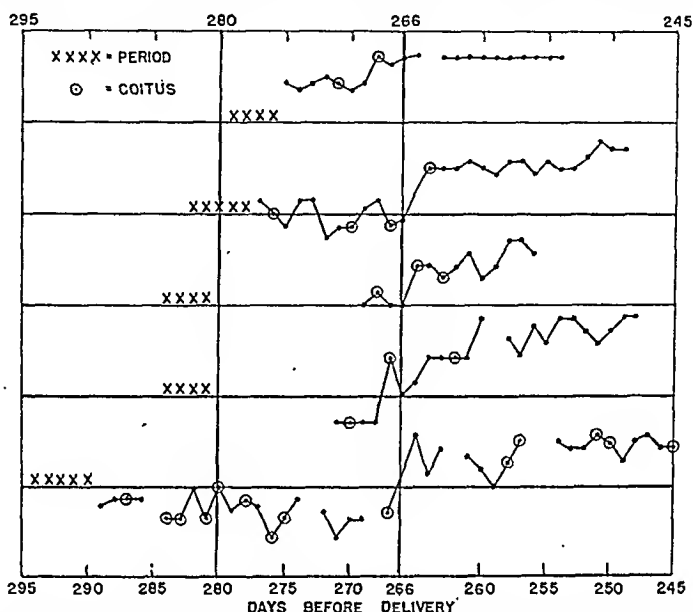


Fig. 183.—Since the interval from the last menstrual period before conception to delivery averages 280 days, and since the woman with regular twenty-eight day cycles ovulates about fourteen days after menstruation, it follows that the interval from ovulation to delivery, or the period of actual gestation, is theoretically 266 days. The chart above is composed of five graphs plotted by "sterility patients" in the course of routine studies. The graphs are aligned to show the actual number of days which intervened from the last menstrual period, and from the temperature shift, to delivery. In none of these cases was labor induced, none had twins, none had babies of less than  $5\frac{1}{2}$  pounds (2500 gm.), none had cesarean sections. It will be seen that the interval from the first day of the menstrual period to delivery was 279, 282, 284, 284 and 294 days, and that the interval from the temperature shift to delivery was 268, 264, 265, 267 and 265 days respectively. It will also be noted that in each case coitus took place close to the time of the temperature shift. The chart may be regarded either as a demonstration of the fact that the temperature shift indicates ovulation, or, if that point be conceded, it may be regarded as confirming the theoretic duration of gestation, namely, 266 days.

is transported by veterinarians over great distances for the purpose of artificial insemination and that the same has been done with human sperm. It is said that in the case of the bat insemination occurs in the autumn and that the sperm survive until ovulation takes place the following spring. Leaving aside conjectural matters it can be said with assurance that, in the human, insemination close to the time of ovulation offers the optimum opportunity for fertilization.

tered if signs of the deficiency supervene. The essential therapeutic need in these patients is a potent anterior pituitary extract such as the thyrotropic factor or a multi-factor extract. Unfortunately, the available anterior pituitary preparations are either of low therapeutic activity, liable to produce antihormones, or unstandardized. The therapeutic problem is complicated and is one of resourcefulness rather than an established program.

#### PITUITARY MYXEDEMA IN CHILDREN

In 1935 Zondek<sup>11</sup> foresaw the possibility of extensive anterior pituitary damage producing a severe form of hypothyroidism in children. The thyroid plays a major role in body development and various manifestations of thyroid deficiencies in children are observed. The age period when the thyroid deficiency begins and the degree of deficiency determine the clinical features. Therefore, the detection of a clinical syndrome in children is more difficult than in adults.

Our first experience with a childhood form of pituitary myxedema was in 1941. Our first patient had been treated as a cretin for a period of thirteen years, whereas Lerman and Stebbins<sup>10</sup> adult case had been treated as myxedema for a period of years. Within a year a total of three patients with childhood pituitary myxedema was observed. In each instance the condition had been previously diagnosed as cretinism. A survey of our own series of cretins revealed that two cases previously diagnosed as cretinism should be reclassified as pituitary myxedema or cretinous pituitarism. The ages of the five patients varied from two and one half to fourteen years. The report of these five cases of infantile pituitary myxedema or cretinous pituitarism follows.

CASE I—The first case was a girl aged fourteen years, who was first examined on April 16, 1941. She had been referred because of retarded growth, retarded puberty, the failure to exhibit the associated psychological advancements of puberty and increasing difficulties with certain study subjects. The patient had been maintained in her age group at school. She had received interrupted thyroid therapy in  $\frac{3}{4}$ -grain daily dosage over a period of years to stimulate growth and general development. She had not responded satisfactorily to this treatment after age nine, and she could tolerate neither continuous thyroid therapy nor increases in dosage to stimulate the retarded growth and sexual development. Finally the mother was advised that since thyroid was ineffective and not tolerated, normal physiological forces would bring about maturity. The mother received the impression that her child was unlike other cretins because of her superior physical and mental condition and the reactions to and the requirements of thyroid therapy. Therefore, the mother had withheld pertinent data of the child's early history and the diagnosis of cretinism because she feared that this data might be prejudicial to the making of a new and possibly a correct diagnosis.

At age eighteen months the child had exhibited what was accepted as evidence of cretinism and this condition had persisted into childhood (Fig. 116).

tion, calculated by this graphic method, is so close to the theoretical 266 days. And it is quite improbable that this degree of consistency between theory and observed fact would be maintained in a larger series of cases.

Basal temperature graphs may also be used to evaluate treatment designed to produce ovulation. Records of patients treated in collaboration with Dr. Paul A. Bishop, Director of the Department of Radiology of the Pennsylvania Hospital, are shown in Figure 184. These results were obtained by using the x-ray technic of Mazer, Baer and Greenberg.<sup>4</sup>

It is now proper to tabulate the reasons for believing that the temperature shift in basal body temperature graphs is a phenomenon associated with ovulation:

#### *Accepted Beliefs*

1. Ovulation occurs about 14 days before menstruation.
2. Conception is most likely to occur if intercourse takes place about the time of ovulation.
3. The average interval between ovulation and delivery is 266 days.
4. X-ray treatment designed to stimulate menstruation must first produce ovulation.

#### *Observations on Graphs*

1. The temperature shift occurs about 14 days before menstruation.
2. Conception is shown to have occurred when intercourse took place about the time of the temperature shift; conversely, pregnancy has not followed when the interval between coitus and the temperature shift has exceeded forty-eight hours.
3. The interval between the temperature shift and delivery averages 266 days in the five cases studied.
4. X-ray treatment for amenorrhea was followed by a temperature shift and about fourteen days later by uterine bleeding.

The reason for the temperature shift is not established. Two suggestions have been made. The first is that the temperature is elevated by progesterone during the latter portion of the cycle. In support of this contention it has been shown that the temperature of postmenopausal patients may be elevated by administration of progestin. The other suggestion is that during the preovulatory phase the temperature is depressed by estrogens. This is said to be analogous to the depression of temperature when stilbestrol is administered during the puerperium. Not only is the cause of the temperature shift undetermined, but the precise relation of the shift to ovulation is also unknown. Examination of a large number of graphs will show that the shift occurs more often after than before the fourteenth premenstrual day. Further, clinical experience shows that coitus shortly before the shift is often fruitful whereas intercourse at a later day in previous cycles has failed. Since the temperature shift is probably a physiologic re-

Physical examination showed a girl of fourteen years, height 52 inches, lower measurement 26 inches, span 53 inches. She was obese and weighed 82 pounds. Her manners, activity and speech appeared to be normal, based on her immature sexual state. The scalp hair was dark, moderately dry, straight and lusterless. The eyebrows were thin, due in part to plucking. The supra-orbital ridges were poorly developed, the nasal bridge was low. The eyes were bright and muscular movements were normal. The skin of the face had a chlorotic type of pallor, and a definite increase of subcutaneous tissue was present. In general all the skin was of this color and dry character. Perspiration was diminished. The teeth were in good condition, the central incisors were of the large boxy type and widely separated and the lateral incisors were small and underdeveloped—the so-called pituitary type of teeth. The hard palate was flat and wide. The voice



Fig 117 (Case I) —A large sella turcica of maximal adult diameter is evident at age of fourteen years

was immature but was neither harsh nor raspy. The facial features and expression were mature in contrast to her general immaturity of development. The thyroid gland was small, about half normal size for her age. The heart was normal and the pulse rate was 68. The breasts had not developed beyond the infantile state and pubic and axillary hair were absent. The external genitals were infantile. The general osseous development was retarded and small for her age. The abdomen was slightly protuberant and umbilical hernia was absent. There was no persistence of lanugous hair on the body. The basal metabolic rate was —19 per cent. Cholesterol was 220 mg per 100 cc of blood.

In summary, the physical examination revealed a child with retarded growth and sexual development whose general mental features combined with the other clinical and physical features were suggestive of anterior pituitary deficiency.

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pituitary and thyroid therapy reestablished the menses and increased height gain

The appearance of the patient at age fifteen and one-half years is shown in Figure 116, *D*

CASE II—The second patient with cretinous pituitarism or pituitary myxedema of infancy was examined on September 17, 1941. This patient was a girl aged three years and four months. The patient had been diagnosed as cretinous during infancy. A tonsillectomy and adenoidectomy was performed at age one and one-half years and the hospital record of this admission stated, "Typical signs of cretinism are present, thyroid extract was resumed"



Fig. 118 (Case II)—X-ray evidence of an eroded sella turcica as large as an adult's at age of three years

Thyroid therapy had not been consistently maintained nor had the child been kept under medical supervision. The parent's opinion was that for ages two to three years she was like other children in appearance and activity except that she grew slowly, and did not require continuous thyroid treatment except when she had attacks of facial swelling and listlessness. After a short period of thyroid therapy she would again become "normal looking." Continuing thyroid therapy always made her restless and nervous. The patient was subject to colds.

At age three years and four months she developed extreme facial and generalized swelling of the skin. She was readmitted for study. She was referred with an X-ray report of markedly enlarged and expanded sella turcica, general osseous retardation and diagnosis of cretinism. Her weight was  $26\frac{1}{4}$  pounds. Her height was that of a two-year-old child, and there was hypotonia (pot-belly), lethargy, delayed dentition, pale dry skin, generalized and prominent subcutaneous infiltration, particularly of the facies.

pitals are using it for study and correlation of findings. The classification is as follows:

- |                               |                                      |
|-------------------------------|--------------------------------------|
| 1. Hypertensive disease       | 4. Eclampsia                         |
| 2. Renal disease              | 5. Vomiting of pregnancy             |
| 3. Preeclampsia, severe; mild | 6. Acute yellow atrophy of the liver |
|                               | 7. Unclassified                      |

To anyone who is interested in obstetrics it is immediately recognizable that a clear-cut distinction between these different conditions is often difficult. There is overlapping between the various groups. Rather mild types of eclampsia can easily pass into the severe type of preeclampsia, and the severe type of preeclampsia can and does develop into eclampsia.

Confusion also occurs frequently in the differentiation of hypertensive disease, preeclampsia and the acute exacerbation of chronic conditions. This differentiation cannot always be made unless the patient is followed not only through the course of pregnancy but also through the postpartum period and for a number of months or even years thereafter. Nevertheless, we have in this classification a satisfactory working basis and its universal adoption for the classification of toxemias is urgently to be sought, in order that some standard may be used throughout the country.

#### THE ETIOLOGY OF TOXEMIA OF PREGNANCY

It has been contended by many that placental infarctions are either the cause of toxemia of pregnancy, or they may be used as a diagnostic criterion of maternal toxemia. Hill and Tremble in 1944 studied the placentas from 640 deliveries which were fixed in 10 per cent formaldehyde solutions for from four to six weeks, then examined closely for certain infarcts involving the placental villi. Forty-two placentas from patients with a definite clinical picture of toxemia were examined but only eight of these had infarcts which were extensive enough to be distinguishable from the placentas of nontoxemic patients. Thirteen of the 598 placentas from patients with normal pregnancies showed infarcts like the eight from the patients with toxemia. Hill and Tremble were unable to satisfy themselves that the acute type of infarct described by Bartholomew and his co-workers was associated with toxemia.

The theory that the posterior pituitary factor plays an important role in the toxemias of pregnancy was presented by Mukherjee in 1941. This investigator relied upon the anatomical observations of Cushing and Ahlstrom that there was morphological evidence of hyperactivation of the neurohypophysis in toxemias of pregnancy, and the biological researches of Anselmino and others pointedly suggested the possibility of such functional hyperactivity.



child was quieter in utero than her four other children. One hour was the average time required to feed him during infancy. His tongue was large and protruded. First dentition occurred at age two years and has continued delayed. A generalized eczema has persisted since infancy. The skin has always been dry, pale, coarse and heavy-looking. General weakness of muscle tone has always been present. He first walked at age three and first talked at age four. His voice has always been deep and raspy. Growth had been very slow and weight gain normal. Sphincter control was established at a normal time.

He had always been an obedient, willing and cooperative child. While a general retardation of mental and physical development was noted early, he entered kindergarten at age five and at age seven he stopped attending school because of retarded progress in scholastic work and a subnormal IQ. A diagnosis of



Fig. 119 (Case III) —Enlargement of the sella turcica at age twelve

cretinism and mongolianism was entered on his school record. His social manners were excellent in spite of the major degree of mental and speech retardation.

His weight increased in spite of a normal intake. The teeth became carious. He had received thyroid during infancy and early childhood but it had been necessary to discontinue thyroid therapy because thyrotoxic symptoms developed before clinical improvement could be established. A few months ago he began to limp.

The general appearance was that of a mentally retarded boy, with retardation of growth and generalized obesity. The facial features were neither typically cretinic nor mongoloid. Weight was 80 pounds and height  $46\frac{1}{8}$  inches. Lower measurement was 21 inches and span  $45\frac{1}{2}$  inches. His statural development was that of a seven and one-half-year-old child with a plus weight of 35 pounds. The scalp hair was dry and coarse. The forehead was high, with eyebrows mod-

est in a group of syphilitic women treated before pregnancy, but not during; slightly higher in patients not treated, since he found the diagnosis of syphilis was actually higher in the group receiving treatment for toxemia during pregnancy.

Peckham thinks that these differences are all within the average of sampling error and the highest incidence in the treated group was well below that of the general clinic population. The amount of treatment employed was without significance. A number of patients had been treated in previous pregnancies without developing toxemia, and others were subsequently treated throughout one or more normal pregnancies. One-half of the treated patients evidenced toxemia before the first injection of an arsenical drug and no correlation was found between the development of physical signs and the specific number of injections previously given.

#### LABORATORY TESTS IN THE TOXEMIAS OF PREGNANCY

It is the consensus that the clinical findings are of much greater importance in the management of toxemia of pregnancy than the laboratory tests. Kriger and Rome, after a study of 652 patients, concluded that an evaluation of renal efficiency with the use of tests for albumin in the urine and urea in the blood did not give sufficient information. High blood urea values occur only when the kidney damage has become pronounced. They also found that the urea concentration excretion and the Fowweather clearance test offered a valuable means for detecting the intermediate as well as gross degrees of kidney damage and give information regarding improvement or deterioration of the kidney function.

Cuizza in 1941 discussed the various tests for functional activity of the liver and kidney and gave in detail the technic for determining Maillard's coefficient.

Cuizza's report is based on eight cases of hyperemesis gravidarum, twenty-six cases of albuminuria and nephropathy in pregnancy, and eight cases of eclampsia. In hyperemesis gravidarum he finds that the organ most seriously injured is the liver as shown by acetonuria, urobilinuria and a high Maillard coefficient, which is a true coefficient of acidosis. On the other hand, kidney function is almost normal as shown by absence of albumin in tests of the urine, normal azotemia and low blood pressure. However, he found that in the nephropathies of pregnancy, kidney function is much more seriously impaired than the function of the liver as shown by albumin, casts in the urine, high azotemia and high blood pressure.

In eclampsia, the function of both the liver and kidneys is seriously impaired. All of the functional tests show more or less deviation from normal. The type of liver injury in eclampsia is different from that in hyperemesis gravidarum, particularly in the absence of acetonuria. The mechanism of the acidosis shown by the high Maillard coefficient differs in the two diseases. In hyperemesis it is due to the accumulation in the blood of ketone bodies which are intermediate products of the abnormal metabolism of fat, while in eclampsia it is due to the accumulation in the blood of intermediate acid products of protein metabolism, among which Zweifel demonstrated sacrolactic acid which was derived from muscle albumins. He believes, therefore, that his study confirms the theory that eclampsia is not merely an aggravated condition of pregnancy nephropathy, but is an essentially different disease marked by pathologic conditions in the liver also. None of the tests used in determining liver and kidney functions is decisive in itself; but

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erately developed. The eyes were bright, and eyelids slightly infiltrated. The extrinsic eye muscles were normal and the inner canthi slanted downwards. The tongue was moderately large and the palate of the broad flat type. The thyroid was small and barely palpable; the heart was negative and the pulse rate 70. The abdomen was protuberant and obese; there was no umbilical hernia. There was subcutaneous infiltration of tissues. Knock knees were present and also a slight limp. The hands were short and spadelike. *Pes planus* was marked. The skin was generally dry, coarse and rough, with generalized chronic eczema. The genitals were underdeveloped. Penis was 2 inches with normal diameter, the testes 1 inch and the scrotum well developed. The basal metabolic rate was  $-31$  per cent.

X rays of the chest showed lung fields clear and the diaphragm, mediastinum and heart configurations were within limits of normal. The epiphyses of the femoral head and neck, as well as the lower end of the femurs about the knee joints and about the wrist joints, showed a condensation and fragmentation resembling x ray appearances of a so-called chondro-osteodystrophy. There was rudimentary development as well as fragmentation of the right and left patella. The size, density and contour of the bones of the cranial vault were compatible with the average normal. Sella turcica was large (Fig. 119) the clinoid processes were of normal density and intact.

The diagnosis in this case is primary anterior pituitary deficiency and secondary hypothyroidism (pituitary myxedema) and an associated primary hypothyroidism.

This patient exhibits a greater degree of hypothyroidism than has been observed in our other cases of the series, however, the case to be described next has an almost equal degree of osseous dysplasia yet the signs of "retarded fetal developmental group" are absent.

The patient's limp was due to a slipped epiphyses which was successfully treated by Dr. DeForest Willard. Thyroxin was given in doses of 0.4 mg. daily to advance epiphyseal development and osseous mobilization of the slipped epiphyses after reduction and plaster cast immobilization. The chronic eczema of more than ten years' duration was cured by the thyroxin, retarded osseous development of the femoral epiphyseal region was advanced towards normal and the slipped epiphyses corrected and permanently immobilized. Physical and genital development have been advanced and at least a stimulus to some degree of mental development obtained.

This case illustrates the actual injustices which followed the failure to distinguish primary hypothyroid cretinism from cretinism developing from a thyrotropic deficiency associated with an extensive or major anterior pituitary deficiency. Primary hypothyroid cretinism beginning in utero is accompanied by irreparable thyroid damage and carries with it an irreparable mental defect in the majority of cases. Anterior pituitary thyrotropic deficiency cretinism is accompanied by a severe involutional or underdeveloped state of the thyroid gland which can be reactivated by specific and/or potent anterior pituitary therapy. It may or may not begin in utero. Our observation of these

patients indicates the mental deficit is not so marked and is in the main reparable with competent therapy

CASE IV—A girl aged nine and one-half years was first examined May 27, 1937. She weighed  $8\frac{1}{2}$  pounds at birth. She was a very sluggish and indifferent feeder, and subject to gastro-intestinal disorders during infancy and early childhood. During the same period she was inactive physically, sluggish mentally and developmentally retarded. First dentition occurred at age three years. She was very late in holding her head up, crawling and she made no attempt to walk until after age three years. Speech was first attempted at three years. Mental de-



Fig 120 (Case IV) —A, Pituitary myxedema in a girl aged eight years B, Same child at age twelve after treatment (see text)

velopment progressed much faster than physical growth. At age five years she was shorter and stouter than her brother aged three years, and at age seven years her brother aged five years surpassed her mentally and physically. Temperamentally she was a quiet and cooperative child.

During infancy the patient had received thyroid therapy. This could not be continuously maintained because of toxic reactions, and she appeared to progress as well without continuous thyroid therapy except in regard to physical development and energy. She was given growth hormone injections and thyroid for a period of a year. This was ineffective and she was referred for treatment of retarded growth and scholastic difficulties.

The patient was  $44\frac{1}{2}$  inches tall (Fig 120, A). The low normal height for

age nine and one half years is 53.7 inches. Her weight was 47½ pounds. Normal weight for her height is 53 pounds. In myxedema the weight is frequently sub normal (Plummer<sup>12</sup>). The lower measurement was 20½ inches and the span was 42½ inches. The head circumference was normal. The scalp hair was well de-

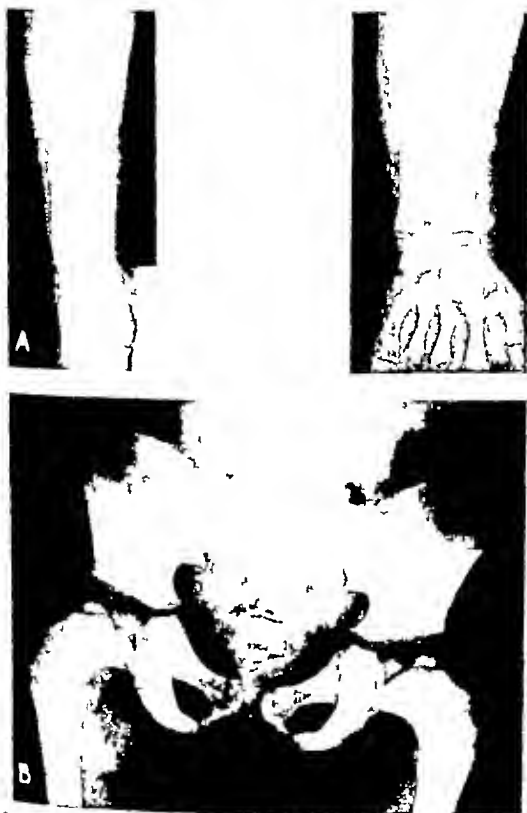


Fig. 191 (Case IV) —Delayed carpal development and underdeveloped femoral head at age of nine years.

veloped, dry and lusterless. Eyebrows, eyelids and the eyes were normal. The facial appearance was oldish; the skin had a yellowish tinted pale color and was dry. The nasal bridge was low and flat. The incisor teeth were of the pituitary deficiency type and generalized caries of the teeth was present. The tongue was

not enlarged The neck was short A small thyroid gland of firm consistency was palpated The heart and lungs were normal and the pulse rate was 72 The abdomen was moderately pot-bellied Umbilical hernia was absent The extremities were short The skin was dry and cool The subcutaneous tissue was excessive

The original diagnosis was pituitary-thyroid deficiency syndrome The physical features were those of pituitary infantilism, however, marked osseous retardation was demonstrated by x-ray (Fig 121) and was primary hypothyroid in character Accordingly it was considered that primary and secondary hypothyroidism coexisted The effect of recent thyroid therapy was evidenced by a recent weight loss of 7 pounds and a blood cholesterol of 198 mg per 100 cc of blood

The patient was given anterior pituitary,  $\frac{1}{2}$  grain, thyroid,  $\frac{1}{10}$  grain, calcium glycerophosphate, 2 grains, three times a day after meals for one year and during this period height gain was established, weight gain was controlled and marked improvement in physical and mental energy and scholastic standing was observed The improvement was so well maintained and progressive that the mother believed further therapy might be avoided and the patient did not report for eight months, at which time she had received no therapy for five months The reasons given for returning to resume therapy were that the growth rate had again become retarded, weight had increased, she was lethargic and her school progress had again been reported as unsatisfactory

Discontinuance of anterior pituitary-thyroid-calcium therapy for six or more months definitely changed the parents' opinion that the child's natural forces would thereafter maintain growth and development The greater the degree of hypothyroidism, i.e., primary thyroid deficiency coexisting with the secondary hypothyroidism of the anterior pituitary deficiency, the more promptly the clinical features recur

Therapy was resumed with  $\frac{1}{3}$  grain of thyroid daily, this was found inadequate and increased to  $\frac{1}{2}$  grain daily At age twelve years therapy was unavoidably interrupted for two months 1 grain of thyroid daily was then given because of pronounced hypothyroid signs Therapy was not maintained and four weeks later the patient's voice was raspy and myxedematous appearance was present One grain of thyroid daily for four weeks caused the disappearance of the raspy voice and myxedematous appearance Anterior pituitary therapy was maintained At twelve years the patient had grown 6 inches (Fig 120, B) Secondary sexual characteristics were still retarded, otherwise her general progress was satisfactory The basal metabolic rate was +28 per cent and the blood cholesterol 280 mg per 100 cc The blood cholesterol was in closer conformity with the clinical picture than the basal metabolic rate In children we have found the blood cholesterol value to be more reliable than the basal metabolic rate

The thyroid was increased to 2 grains a day and continued at this dosage for one year. At age fourteen years the patient had not menstruated nor had breast development advanced. There was slight pubic hair growth. Her pulse was rapid and the thyroid was reduced to 1 grain daily and anterior pituitary was again increased to 2 grains daily. Breast development advanced and menarche occurred three months later. The thyroid gland, which had been very small originally, had developed to normal size but it was of the firm hypoplastic type. The patient has continued to show normal advancement under therapy, and at age fifteen years she is perfectly normal in appearance and menstruates regularly. A review of her clinical record and responses to therapy indicates that this patient was also a case of pituitary cretinism.

**CASE V**—A male child was first examined by the referring physician at age two, at which time he exhibited the typical physical features of cretinism (Fig 122 A) and the early history was typical of cretinism. At this time the child was given 2 grains of thyroid and in two weeks the cretinic swelling of his face began to disappear. In three months the cretinic features had disappeared (Fig 122 B) and he became generally more mentally and physically alert. From age two to five and one half years, when he was referred to me, the patient would receive from 2 to 4 grains of thyroid daily for a few months and then thyroid would have to be discontinued because nervousness and restlessness developed and management of him would become extremely difficult. The only complaint at the time of referral was that he does not appear to recognize the word obey. His memory is good he talks 'right well and he gets along very well with his age group."

The physical examination revealed a boy five and one-half years of age, whose weight was 40½ pounds (low normal 37.4 pounds). Height was 41½ inches (low normal 42.4 inches). Lower measurement was 20¾ inches (low normal 19.3 inches). Circumference of the head was 19½ inches (low normal 20.4 inches). The shape of the head was normal and the scalp hair was dark, fine and of moderate thickness. The eyes were dark, bright, active; eyes muscles and pupils reacted normally. Eyebrows, eyelids and tongue were normal and the palate showed a high vault with a circular elevation in the midcentral region. The voice was normal and the speech good. A normal number of teeth was present, but they were extremely small and square and showed marginal darkening. The thyroid was slightly palpable. The heart sound and rate were normal. The lungs were normal. There was no umbilical hernia. The penis was infantile, the testes extremely hypoplastic, and the scrotum underdeveloped. The extremities were lean, with good musculature. Lanuginous hair was absent. The skin had a soft texture with no evidence of dryness or pigmentation. Perspiration was normal.

The physical examination was normal except for a small height deficit based on lowest normal height for his age and the hypogonadism. The mental activity was reasonably normal for his age. The patient was well behaved and cooperative. The only (gross) abnormality present was hypogonadism. The patient had been referred as a behavior problem, otherwise the parents were well pleased with the child's progress under interrupted thyroid therapy.

The following therapy was advised: anterior pituitary extract, 2 grains, thyroid, 1 grain, calcium glycerophosphate, 6 grains, daily in two divided doses.



The child showed a very satisfactory response to this therapy, his behavior improved and he was less restless and more cooperative. He had been receiving from 3 to 4 grains of thyroid, it is quite probable that the reduction in the dosage of thyroid accounted for his improved behavior. This therapy was maintained and his mental and physical development progressed satisfactorily. The dosages were adjusted to his progress and ultimately 2 grains of thyroid produced nervousness, restlessness and uncooperativeness, thyroid was then reduced to 1 grain and these symptoms disappeared.

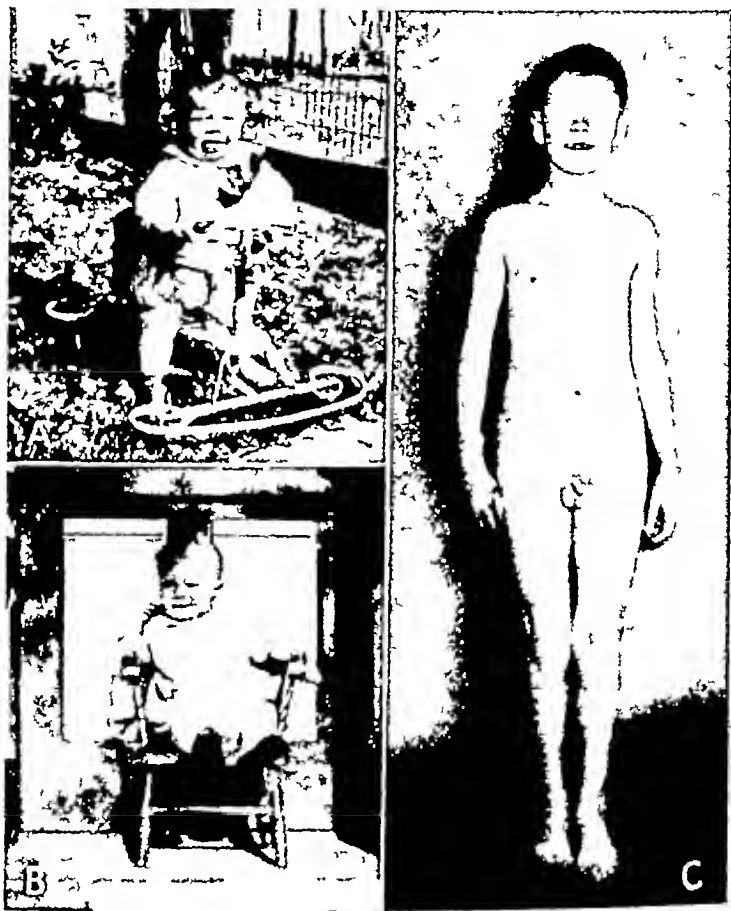


Fig. 122 (Case V) —Pituitary myxedema diagnosed as cretinism. *A*, Patient at age of two years. *B*, Two months later after thyroid therapy. The cretinic features have disappeared. *C*, At age twelve, after thyroid and anterior pituitary therapy.

The boy entered school at age seven years. For periods of from five months to one and one-half years he was given exclusively interrupted thyroid therapy without medical supervision. The parents' opinion was that he was "doing all right" and his retarded growth was considered a "family trait." A visit would be made for "pepping up" and anterior pituitary-thyroid and calcium therapy would be resumed for four to six months, and then only thyroid would be given by the parents.

During the administration of the anterior pituitary and thyroid, his general effectiveness, physical and mental improved, and height gain and genital development were advanced and weight was better controlled than with thyroid alone

Our first suspicion that the diagnosis of cretinism in this case was incorrect occurred when at age eleven years (Fig 122, C) the patient won a spelling bee in competition with 43 pupils. This event occurred following a 'pepping up' visit. Originally we did not consider this case as one of pituitary cretinism because the initial clinical appearance and findings and the response to thyroid therapy were typically cretinic. The hypothyroidism now appears to be due to an anterior pituitary thyrotropic deficiency.

The interpretation of the nature of the endocrinous deficiency existing in this case is supported by the patient's incomplete response to thyroid exclusively and a complete response to combined oral anterior pituitary and thyroid therapy. Study of the patient's growth graph reveals that thyroid alone did not maintain a normal growth rate. At age five and one half years he had a growth deficit of less than an inch below the *low normal* for his age. When oral anterior pituitary and thyroid therapy was fairly well maintained during ages five and one half to seven and one half years, a low normal height value for his age was attained. In the succeeding one and one half years, during the age period when a male child normally exhibits his best maximal growth rate, he received only thyroid extract in dosage just below tolerance, yet his growth curve lagged to the extent that there was an  $1\frac{1}{2}$  inch deficit below low normal for his age. Resumption of oral anterior pituitary therapy and male hormone or anterior pituitary and thyroid again stimulated growth and produced a satisfactory growth curve. Whenever growth stimulation abated or ceased weight gain occurred, and only when weight gain was controlled at a normal level was a height gain at a normal rate obtained.

I have now reclassified this case as one of pituitary cretinism or myxedema. The change in diagnosis is based upon observing similar clinical, therapeutic and developmental events in four cases of pituitary cretinism. The events observed in this case correspond to those in the four cases already cited of unquestionable pituitary myxedema in childhood. We have been unable to obtain x-ray studies of the patient's sella turcica.

#### COMMENT

There is no evidence that the hypodermic administration of anterior pituitary preparations produces therapeutic results but their oral administration has done so. All the cases were treated with anterior pituitary and low dosage of thyroid or thyroxin and calcium glycerophosphate. The anterior pituitary and thyroid glands normally increase their physiological activity to meet the increased requirements

of body development. If thyroid dosage is maintained above the level of deficiency the excess covers the body's increased requirements and the thyroid gland will not respond physiologically as it normally should, therefore thyroid dosage is maintained as low as possible in order that the thyroid gland will react to body stimuli.

Complete x-ray studies should be made in all patients with myxedema and cretinism when first examined. Enlargement of the sella turcica will probably not be found consistently in all cases of pituitary myxedema or cretinous pituitarism. Extensive degeneration of the anterior lobe may occur without creating intra sella pressure and enlargement of the sella turcica. The presence of an enlarged sella turcica and osseous pathology of the type observed in our young patients, the absence of signs of retarded fetal development in the physical examination and a very rapid therapeutic response to thyroid should cause one to give earnest consideration to the diagnosis of cretinous pituitarism in preference to cretinism. The two conditions can be clinically differentiated in spite of their striking early similarity in facial appearance, and in physical and mental retardation, symptoms which have the common etiological factor, hypothyroidism. The physical signs of retarded fetal development are absent in cretinous pituitarism.

The hypothyroidism of cretinous pituitarism and pituitary myxedema of adults is due to secondary hypothyroidism, which is a result of the partial or total failure of the anterior lobe to produce the thyrotropic factor and the resultant biologic atrophy of the thyroid. Cretinism is due to primary hypothyroidism and is the result of primary damage within the thyroid, aplasia, absence or progressive degeneration of the thyroid. In cretinous pituitarism and adult pituitary myxedema the thyroid can be reactivated by proper anterior pituitary therapy. In young patients, as age advances normal physiological hypertrophy of the thyroid occurs and improved function is possible. The thyroid of the cretin is beyond stimulation or rehabilitation.

X-ray studies show extensive osseous retardation and osseous pathology in epiphyseal areas in infantile pituitary myxedema and *an adult size or extremely enlarged sella turcica* (see Figs 117, 118 and 119). Patients with cretinous pituitarism exhibit definite signs of growth and gonadal deficiency as well as thyroid deficiency. In adult pituitary myxedema, gonadal deficiency and adrenal cortical deficiency are likely to occur. Adrenal cortical deficiency is less of a factor in childhood because of the normally large adrenal glands present during these age periods. The gonadal deficiency of cretinous pituitarism appears to remain more constant because of the anterior pituitary deficiency, whereas in cretinism sexual development often progresses to maturity because the anterior pituitary is not involved.

Exclusive thyroid therapy rapidly changes the cretinic facies to normal (see Fig 122, B) and improves osseous development of cretinous pituitarism but growth and gonadal deficiency are unsatisfactorily

affected The continuous oral administration of anterior pituitary combined with thyroid in low dosage to patients having cretinous pituitarism will satisfactorily develop the gonads, advance osseous development, stimulate growth and improve thyroid function

The mental activity and functions of the patients having cretinous pituitarism can be advanced and maintained at a satisfactory normal level by endocrinous therapy whereas the cretin cannot be advanced to normal because of the inherent defect in mental development. The mental advancement obtainable in cretinous pituitarism with proper endocrine therapy makes its differential diagnosis from cretinism of great importance to both the parents and the child in so far as their ultimate social and economic status is concerned

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# RABIES SOME PRACTICAL QUESTIONS AND ANSWERS

CAPTAIN RICHARD A. KERN\*

MEDICAL CORPS, VOLUNTEER SERVICE (SPECIAL), UNITED STATES NAVAL RESERVE

RABIES does not constitute a major public health problem in this country, the annual number of human cases now averages slightly under 100. But in the individual patient who has just been bitten by a dog, the possibility of rabies suddenly becomes a very serious matter, since the disease, once developed in man, is always fatal. Not only have most physicians never seen a case of rabies, but many have never treated a case of dog-bite. When such a circumstance arises, their meager practical knowledge of the subject engenders a correspondingly avid interest that ordinary textbooks often fail to satisfy. The writing of this article was suggested by the many urgent questions about rabies in general, and the doctor's problems in particular, that have been put to the author, usually over the telephone, because of his connection with a board of health. This paper contains little that is new or original, it has drawn freely on various publications mentioned in the bibliography. Its justification lies in its making the answers to such questions more readily available to questioners, not only at home, but in the field and away from their usual sources of information.

**What is rabies?**—Rabies can be briefly defined as an acute infectious disease of certain lower animals, it is caused by a neurotropic filtrable virus, occurring in the saliva, in the salivary glands and certain nervous tissues. The virus is transmissible by bite, rarely by contamination of an open wound by infected saliva or infected tissue, also by direct inoculation of infected tissues, and causes a disease characterized pathologically by changes especially in the motor nerve cells of the basal nuclei and cord, and clinically by a long period of incubation, a stage of excitement, a paralytic stage and death.

**What are the sources of rabies infection in man?**—Rabies is primarily a disease of the canine family (dogs, wolves, foxes, coyotes, hvenas, jackals, etc.) Canines bite—their teeth are their sole weapons of offense and defense. Canines fight not merely in self-defense, but for the sheer love of fighting. Since most mammals, including man, are susceptible to rabies, and since canines bite many of these, rabies is thus transmitted to man and to many other species. Canines frequently bite

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The opinions or assertions contained herein are the private ones of the writer and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

\* Vice-President, Board of Health, Lower Merion Township, Montgomery County, Pennsylvania

members of their own species. Since the incubation period in dogs may be ninety or more days, as few as four infected dogs a year could maintain a reservoir of infection. Rabid canines are therefore overwhelmingly responsible both for the transmission of the disease to man and other species and for the continuation of the disease in their own family.

Human rabies arises in nearly 90 per cent of cases from a canine source. About 10 per cent have a feline origin. (Most feline rabies is of canine origin). Occasionally man is infected by a horse, mule, cow, skunk, squirrel, sheep, pig or other animal previously bitten by a rabid dog. Rabies has never been known to be transmitted from man to man, nor has a rabid man ever made news by biting a dog.

In addition to canines and felines, only one other group of animals has been known to play an active role in rabies transmission—certain *blood sucking* bats of Central and South America. For the benefit of service personnel, it must be emphatically stated that these do not include the large bats (flying foxes) of the South Pacific, the latter are primarily fruit-eating. Nor, fortunately, do rats seem to be involved, pugnacious, widespread and susceptible to infection as they are. Their small size and probably the increased virulence of the infection in rodents insure a short incubation period so that the disease dies out with the infected individual before a reservoir can be established in the colony.

The canine reservoir of infection may be subdivided into *domestic* (dogs) and *wild* (wolves, foxes, etc.) In Russia, wolves have long played an important part in the continuance of rabies. In North America, coyotes have occasionally been responsible for outbreaks, notably in cattle. General Simcoe, the first Lieutenant-Governor of Upper Canada, died in Exeter, England, in 1806 from the bite of a rabid fox. But in all parts of the world, clinical experience and efforts to control rabies have shown the wild reservoir to be of very minor and dwindling importance, dogs are the only important means of continuance and transmission of the disease.

**How prevalent is rabies?**—Rabies in lower animals, and consequently in man, varies in frequency in different parts of the world. It has never been found in Australia and New Zealand. There has been no rabies in England since 1923. It is rare in the Scandinavian countries, in Holland, Germany and Switzerland. Rabies is more or less common in Belgium, France, Italy, Russia, China, India, Indo China, Japan and the Dutch East Indies.

Rabies is now found in all parts of the United States, and according to available figures is increasing in some areas. Local outbreaks occur from time to time. In 1937, 2000 rabid animals and three human cases were found in California. There were ten human deaths from rabies in Illinois in 1936. In 1938, 493 rabid animals were seen in Pennsylvania, 365 of them in Philadelphia. Montgomery, Delaware, Chester and

Bucks counties Texas and California have in recent years furnished the most rabid animals, and Texas and Tennessee the most human cases of rabies.

The prevalence of rabies in any country is a function of the existence and enforcement of laws for the control of rabies in dogs. There have been no human deaths from rabies in England since 1903, there have been over 3000 in the United States in that time.

*Is rabies a seasonal disease?*—Rabies occurs at any time of the year. There is no relation between rabies and the so-called "dog days."

*What are the chances of infection if a person is bitten by a rabid dog?*—About 16 per cent of all such bites will result in human rabies in the absence of any preventive measures. But in the individual case the chances vary widely, depending on these factors:

- 1 The number of bites
- 2 The type of wound. Deep puncture wounds and badly lacerated wounds are more dangerous.
- 3 Whether the bitten part was covered or bare. Clothing tends to clean the tooth before it penetrates.
- 4 The animal inflicting the bite. The danger decreases in this order: wolves, cats, dogs, other animals.

On the basis of data gathered in Pasteur Institutes in Europe, Babes<sup>1</sup> cites the following table of probabilities of infection under the given circumstances:

Type and Location of Wound	Animal Causing Wound	Chances of Infection, Per Cent
Multiple, deep eye, nose, lips	Wolf	100
" " " " "	Cat	70
" " " " "	Dog	60
" " rest of face	Dog	50
" " rest of bare areas	Dog	30
Single, deep, fingers, neck	Dog	15
Superficial uncovered areas	Dog	10
(but if these bleed freely)	Dog	2
Infected saliva on a recent wound		0.1
" " " " 24-hour-old wound		0

Human rabies occurs most often among those who are most likely to come in contact with infected animals by reason of occupation (farmers, veterinarians) or ownership. Infection frequently happens when there is as yet no suspicion of rabies in the animal, which is being examined, because of dysphagia, for a possible foreign body in the throat. A bite on the thumb is easily incurred and, if it be through the thumb nail, is hard to treat properly. Infection of laboratory workers has occurred in the course of dissecting the head of a rabid animal. Although it is theoretically possible that infected saliva on objects such as toys, furniture, rugs, etc., might infect a handler with an open wound, the drying of the saliva makes that contingency

exceedingly remote, no case of such means of infection has ever been recorded

When is a dog infective?—The virus appears in increasing amounts in the infected dog's saliva during the last five to eight days of the incubation period and is abundantly present during the active illness up to the time of death. The earliest observed appearance of virus in the saliva before the dog became obviously ill was reported by Zagorra<sup>12</sup> to be twelve days. This fact accounts for two axioms of paramount importance: first, that the dog may appear to be perfectly well at a time when his bite is infective, and second, that a bitten person is safe from rabies, even though the dog dies of that disease, provided that the bite was inflicted fourteen days before the dog developed symptoms.

What is the incubation period of rabies?—It varies with the strain of virus (see below) and with the distance between the location of the bite and the central nervous system, to which the virus travels along the peripheral nerves. Therefore the incubation period is shortest for bites on the face and longest for bites on the foot. It is shorter in children than in adults. It is shorter in dogs than in humans. The extremes observed in man are from as low as twelve days after a face bite up to eleven months after a bite on the foot. The incubation period for most human cases falls between twenty and ninety days. In dogs the extremes are between twelve and one hundred-thirteen days,<sup>7</sup> with most cases falling between twenty and forty days.

#### SYMPTOMS AND DIAGNOSIS

What are the symptoms of rabies?—In man, there is a stage of excitement, based on irritative motor lesions in the central nervous system. These are first apparent in the throat muscles, later they become generalized. There are periods of convulsive contractions alternating with free intervals. The spasm of the throat muscles is precipitated by attempts to swallow, making swallowing impossible and giving rise to an unwillingness to try to swallow food or water, not a fear of water (hydrophobia). The patient early has some difficulty in breathing, with a tendency to a gasping type of inspiration. As the disease progresses, the muscular spasms become more diffuse until they may involve the whole body. Reflexes are increased and the pupils are at first contracted, later dilated and fixed. Eventually this stage gives way to a terminal paralytic phase, with a flaccid paralysis of affected muscle groups. There is a moderate leukocytosis, a rising fever and pulse rate. Death occurs usually during the third or fourth day. It may occur during a convulsion or after the onset of the paralytic stage, through involvement of the heart or the respiratory center. A particularly distressing feature of the human disease is the clear sensorium and mental anguish of the patient between convulsions and even after paralysis has set in. For a vivid description of the clinical course in twelve cases seen at the Cook County Hospital, Chicago



illustrated by photographs, the reader is referred to the report of Blatt, Hoffman and Schneider<sup>2</sup>

The *differential diagnosis* involves chiefly three diseases tetanus, botulism and hysteria. Tetanus rarely results from a bite, and trismus in tetanus is usually the first symptom and is constant, not intermittent. In botulism, the involvement of the ocular muscles (diplopia) is characteristic. Hysteria (lyssophobia) may mimic true rabies or the patient's notion of what rabies should be (growling, frothing at the mouth), but it comes on too soon after the bite, long before even the shortest possible incubation period could have elapsed.

In the dog, the same two stages may occur: stage of excitement (furious rabies) and paralytic stage (dumb rabies). The *stage of excitement* is less constant in occurrence and more variable in type in dogs than in man. Most common in this stage are changes in behavior and temperament. A home-loving dog becomes restless and runs far and aimlessly. In a case in our experience the dog was caught over thirty miles from home, his path marked by a trail of half-a-dozen bitten dogs. An affectionate dog becomes ill-tempered and aggressive and bites its master. A quiet animal may become unduly demonstrative and fawn excessively upon the members of the household. Strange appetites and cravings are manifested as the animal rejects its food but chews on pieces of wood or stone, rugs, etc. Convulsive spasms of the throat muscles produce trouble in swallowing food and in drinking. The dog growls, barks hoarsely and snaps aimlessly at things in its path. Generalized convulsions occur as the disease advances. The *paralytic stage* following the stage of excitement may quickly terminate the picture, or in many cases it may be the only stage. In dumb rabies the animal is quiet, secretive, often increasingly affectionate. The paralysis commonly appears first in the muscles of the jaw which hangs down, tongue protruding and drooling saliva. Later other muscle groups, notably those of the hind quarters, are affected and the dog lies helpless. Death in canine rabies occurs in from two to five days after the onset of symptoms.

#### PREVENTION AND TREATMENT

What is the treatment of rabies?—Nothing beyond palliation. Once rabies has developed, it is always fatal.

What steps shall be taken to prevent rabies in a case of dog bite?

1. Catch the dog and place it in observation quarantine in an approved veterinary hospital. *Never shoot the dog.*
2. Give proper attention to the wound.
3. If indicated, give Pasteur treatment.

What should be done to the wound?—First, the wound should be *freely opened*, so that all parts are accessible, and bleeding should be encouraged. Next, in spite of much discussion to the contrary, it is wise to *cauterize* the wound. The Romans knew that the application of the

actual cautery greatly reduced the incidence of human rabies after bites by rabid animals. Now chemical cauterization is practiced, preferably with fuming nitric acid. Surgeons are often unwilling to cauterize dog bites, especially on the face and in females, because of scarring. Yet face bites are particularly in need of cauterization, since the incubation period may be too short for Pasteur treatment to be effective. Moreover, Pasteur treatment alone is not always effective, regardless of the site of the bite. Cauterization with nitric acid performed early prevents infection in experimental animals, as shown by Rosenau.<sup>11</sup> Cauterization is available within minutes and is effective within twenty-four hours or even longer, whereas a day or two may elapse before Pasteur treatment can be started. It is gross negligence not to cauterize a face bite at a time when rabies has been reported in an animal in the community within one hundred days. Paul<sup>12</sup> advises that the acid should be applied drop by drop from a capillary pipette, taking pains to bring the acid in contact with every part of the wound, but carefully avoiding getting acid on sound skin. Wounds made by rabid animals should not be closely sutured. Veterinarians should be warned against frequent carelessness in the matter of attention to their own wounds incurred in their practice.

What are the indications for Pasteur treatment?

A. Pasteur treatment should be started at once

- 1 If the dog is obviously rabid
- 2 If the dog got away, he may have been rabid
- 3 If the dog was shot just after he bit, he may have been in the incubative stage with virus in the saliva, but before Negri bodies had appeared in the brain
- 4 If the bite is on the face or neck, the incubation period of such bites is too short to wait to see if the dog develops rabies within two weeks. In such a case the treatment may be stopped at the end of fourteen days after the bite, if the dog is still well
- 5 If the laboratory to which the dog's head was sent for diagnosis reports that the brain was too decayed to examine (heads must be packed in ice)
- 6 If the saliva of a rabid animal gets into a fresh wound (less than twenty-four hours old)
- 7 If a dog known to be rabid has licked the face of a very young child or infant.

B. If the dog is apprehended, he should be kept under observation and securely chained in an approved veterinary hospital for fourteen days

- 1 If at the end of fourteen days the dog is still well his bite could not have been infective so Pasteur treatment need not be given, and in case it had been started because of a face or neck bite, the treatment may be stopped

- 2 If the dog dies before the fourteen days are over, the head should be severed at once, packed in ice, and sent to the state laboratory for diagnosis. If the laboratory gives a positive report, or if the veterinarian makes a clinical diagnosis of rabies, Pasteur treatment should be started at once.

What is the principle underlying Pasteur treatment?—Pasteur found that when the virus from the rabid dog ("street" virus) is passed repeatedly through rabbits, it becomes much more virulent for rabbits and its incubation period is shortened until it remains fixed at six or seven days ("fixed" virus). It is definitely less virulent for man than is "street" virus. Moreover, this "fixed" virus as contained in the spinal cord of a rabbit dead from the infection can be attenuated by drying under sterile precautions in a flask containing caustic potash. If removed after twenty-four hours, the cord is almost as active as fresh material, after forty-eight hours, it is clearly less so, and by the end of eight days it is inert. Yet it has not wholly lost its antigenic powers. Pasteur found that animals and man could be protected against "street" virus infection by inducing an active immunity by a daily injection of an emulsion of rabbit-cord containing "fixed" virus, beginning with a cord dried for fourteen days, followed on succeeding days with cords dried one day less. The total number of injections is usually fourteen, although in case of severe multiple bites, especially if involving the head, a twenty-one day course is advised. The basic points in the treatment are the fact that the incubation period of "fixed" virus infection is shorter than that of "street" virus, and that attenuation of the "fixed" virus by drying makes its injection into man safe without destroying its power to stimulate the production of immune substances.

What are the results of Pasteur treatment?—The figures published by McKendrick<sup>4</sup> in 1934 are characteristic. In a series of 69,541 persons who received Pasteur treatment after having been bitten by animals known to be rabid, the mortality was 0.23 per cent. It must be remembered that without treatment the expected mortality is 16 per cent.

Are there any risks involved in Pasteur treatment?—Some treated patients develop an involvement of the nervous system ranging from a peripheral neuritis to a severe myelitis with paralysis that may prove fatal. McCoy<sup>5</sup> reported six cases of paralysis among 37,500 persons treated, an incidence of less than 0.016 per cent. Among such paralytic cases the mortality is 16 per cent, the rest usually recovering completely. The risk of incurring rabies is so much greater than that of incurring paralysis that the latter danger is not a valid argument against the use of the treatments. Moreover, as McCoy emphasizes, the treatment should be carried to completion, even though myelitis has set in.

Are there any contraindications to Pasteur treatment?—There are none.

Rosenau<sup>11</sup> reports no ill effects when the treatment is given to pregnant women.

How long does the immunity produced by Pasteur treatment last?—About a year. A suspicious bite after that time calls for a new course of treatment.

### CONTROL OF RABIES

What is the possibility of immunizing dogs by some form of rabies vaccine?—The answer to this question resolves itself into two phases *after* and *before* a bite by a rabid animal.

1 *After* a dog has been so bitten it is practically useless to attempt Pasteur treatment as in man, because of the shorter incubation period in the dog, and particularly because a dog is likely to incur multiple bites on the head and neck.

2 *Before* a bite by a rabid animal, dogs can be protected against rabies by proper immunization. At first glance, the solution of the entire rabies problem would seem to lie in the application of such immunization to all dogs. Unfortunately, the cost of such immunization is prohibitive. The material for the fourteen-dose human Pasteur treatment costs about seven dollars. As a result, various modifications have been made, chiefly by the manufacturers of veterinary biologicals, in the direction of lowered cost by reducing the number of doses to be given. The immunizing value of such treatments is directly proportional to the number of doses used. Dogs given multiple injections remain immune for at least a year, and some remained immune in Pasteur's experience, as cited by Ravenel,<sup>10</sup> for several years, one dog as long as five years. As Lentz<sup>4</sup> has shown experimentally, the single-dose method is probably worthless. Yet it is being extensively used by the dog licensing authorities of certain states as part of a program of rabies control. The chief objection to the procedure lies in the false sense of security which it engenders in the owners of dogs. Hart and Evans<sup>8</sup> reported the instance of a man who was bitten on the face by a neighbor's dog which was fighting with and had bitten his own dog. Since both dogs had been given a single dose of rabies vaccine within six months, no special precautions were taken. A few days later, the biting dog was accidentally killed by an automobile. The bitten dog and his owner both died of rabies. Five-dose courses of treatment probably offer good protection if repeated yearly, but their cost still precludes universal application.

What is the outlook for eradicating rabies in the United States?—It is agreed by competent authorities <sup>8 10 11,12</sup> that rabies could be eliminated from this country in the course of three or four years by a properly planned and enforced program. It is therefore all the more regrettable that the present outlook for achieving this end is virtually hopeless. A workable program must include at least nation-wide co-

operation, if not actually nation-wide control yet it is practically impossible to pass and *enforce* effective dog laws in local communities, let alone a whole state. In Pennsylvania the Department of Public Health was never able to secure the passage of a dog law to protect the human population against rabies. Not until enough sheep and cattle died from bites by rabid dogs so that the farmers were aroused was any action taken. Then the dog laws were passed at the instigation of the Department of Agriculture, which still administers those laws and to which the income from dog licenses accrues, chiefly to indemnify farmers for sheep and cattle destroyed by dogs.

At present the attempt to control rabies in the United States is minutely divided into local efforts that are an index of the health consciousness of the individual community, township, county or state. Some communities are doing excellent work, but this is constantly being set at naught by the poor work of a careless neighbor. For the most part little attention is paid by most health departments to rabies control until a sharp outbreak of the disease in animals or a human fatality excites a spasm of activity, usually heralded by the newspaper headline of a "dog quarantine." But the activity is soon ended, with the tacit consent of an apathetic majority and under the pressure of a small but highly voluble minority, the so-called "dog-lovers," who actively oppose any effective measure of control. The algebraic sum of control effort is therefore practically zero.

What measures constitute a proper rabies control program?—In order to eliminate the disease from this country it will be necessary to enforce certain measures uniformly and on a nation-wide scale. Moreover, some measures, those involving the restriction of activity of dogs, must be more stringent during the period of elimination (perhaps three years) than need be the case thereafter. Some measures, such as canine immigration quarantine, must never be relaxed. The important measures are these:

1 *The enforced licensing of all dogs.* This has the prime purpose of fixing the human responsibility.

2 *The elimination of stray dogs.* This does not refer alone to the ownerless dog. It is equally applicable to the pet which is allowed to roam at will, be he licensed and muzzled or not (except as later noted). Neither license nor muzzle will protect such a pet from a bite by another roaming dog without a muzzle. "Roaming at will" means that the dog is neither on a leash nor accompanied by a master who by word or call can control his actions.

All stray dogs as above defined must be caught and impounded. The catching program must be active at least six days a week, including occasional Sundays. It should also be carried on at times as late as midnight to catch dogs allowed to run loose after dark. If the impounded dog is unlicensed, he should be kept for seventy-two hours to permit an owner to claim him. (He may be licensed, but may have

slipped his collar ) If unclaimed, the dog should be destroyed. If the dog is licensed, the owner should be notified and fined, with a rising scale of fines for repeated offenses.

3 *Muzzling of dogs* permitted to be at large is an expedient the value of which has been much debated, the opinions ranging all the way from the claim that it could succeed by itself in wiping out rabies to the statement that it is useless. The truth lies somewhere between these extremes. Muzzling alone could not be successful, for the unmuzzled ownerless dog would keep the infection going in all dogs, whether muzzled or not. Moreover, the human infections would still continue, since they arise chiefly in those who handle their own pets which have become ill. Furthermore, muzzling does not always succeed in preventing bites, for it is difficult successfully to muzzle short-nosed breeds. But muzzling would greatly reduce the number of dog-bite cases calling for treatment in humans. It would also greatly reduce the chances of rabies transmission *after* unmuzzled strays had been eliminated from the country for a sufficiently long period. Certainly experience in England has shown the value of muzzling as an adjuvant measure in rabies control. It might therefore be used as a part of the control program under these conditions. When, as a result of the complete elimination of strays and the enforcement of immigration quarantine (see below), no case of rabies in an animal has been reported for 180 days, then licensed dogs can safely be allowed to be at large, provided they go muzzled. This would make it possible partly to overcome the greatest difficulty encountered in this work—the unwillingness of dog owners to keep their dogs constantly under complete restraint. If and when a case of rabies in an animal re-appeared, complete restraint would again have to be enforced for a period of 180 days. If and when no rabies had occurred for two years, dogs could be at large unmuzzled.

4 *Quarantine on canine immigration* is indispensable and must be a permanent part of rabies control. It must be a federal measure. England has wisely and rigidly adhered to a 180-day observation quarantine on all dogs brought into the country. Penalties for attempted avoidance of quarantine include a fine of £125. Neither sentiment nor favor has been permitted to interfere with the enforcement of the law. Several years ago our newspapers unsuccessfully belabored the application of the rule to the "seeing-eye" dog of a blind American tourist. Only recently it was reported that the pet dog of General Eisenhower had been released at the end of its 180-day quarantine. Just after the last war, rabies was re-introduced into England by a dog smuggled into the country in an airplane by a returning soldier; it took nearly three years to eradicate the disease again.

5 *Immunization of dogs* is of value only if it is carried out by a course of at least five doses of a good rabies vaccine, and if it is repeated once or twice at intervals of a year. Its application is therefore

limited in scope, but a comforting measure in case of valuable pets

6 *The intelligent and active cooperation of the public* is the most important factor in rabies control, for without such cooperation it is difficult to enact and impossible to enforce the control measures previously mentioned. Yet at present there is virtually no such cooperation. Our opinions are based on what we experience first-hand, on what we hear, or on what we see in print. Rabies is comparatively so rare that it comes actively to the attention of only a very few people. As a result, not only the great majority of laymen but most physicians give little or no thought to the matter. They view with apathy the occasional efforts at control by local health authorities.

What is worse, a small minority who are dog-owners strenuously oppose any effective control measures. They are loud in their protestations against restricting the liberty of their pets, which, they feel, should be allowed to wander as they please. When rabies is mentioned, they commonly claim that there really is no such disease, and that the alleged symptoms are the hysterical reactions of the bitten person, suggested by mendacious propaganda of physicians and veterinarians. They may even actively interfere with law enforcement, as in our community where one such person at times acts as an outrider to warn the suburb that the dog catcher is coming up the street.

Members of health and of police departments therefore not only get little encouragement in their efforts at rabies control, but find themselves at times the objects of open attack. Even when a case of dog-bite or of canine rabies suddenly inspires an anti-rabies crusade in a single household, it is usually productive of little beyond a complaint to the Board of Health ("Why don't you *do* something?") Limited budgets and lack of equipment all too frequently diminish or end the local effort.

Yet the elimination of rabies from the land should be earnestly advocated. For not only is it scientifically feasible, but it is economically sound. Quite apart from the saving of human life, the money saved by preventing the loss of considerable numbers of cattle, horses and other domestic animals would in a few years offset the initial cost of eliminating rabies and thereafter would easily outbalance the cost of keeping the disease out of the country.

Therefore it is to be hoped that a concerted and continued attempt at rabies control will be inaugurated under federal guidance. It should be a campaign with a long-range view, careful planning and correlation of legal machinery and control procedure throughout the country. And particularly it should include a sustained program of education and information by all available means, including press and radio. Rabies control and elimination can then be achieved and maintained under the impetus of an enlightened public opinion.

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# OBSERVATIONS ON THE EPIDEMIOLOGY AND BACTERIOLOGY OF ACUTE RESPIRATORY TRACT INFECTIONS AMONG THE ARMED FORCES OF THE TROPICAL SOUTH PACIFIC

LT COMMANDER ROBERT F NORRIS

MEDICAL CORPS, UNITED STATES NAVAL RESERVE

DURING a recent tour of duty on board a United States Naval Hospital Ship in the South Pacific, it was found that acute infections of the upper respiratory tract were prevalent among our armed forces and the morbidity rate was sufficiently high to be of military interest. In addition, the basic bacteriologic flora of the nasopharynx differed from that ordinarily reported in temperate zones and from that previously reported in other regions of the tropics. The rarity of the pneumococcus was especially striking. The details of these studies have been previously published <sup>1, 2</sup>

## EPIDEMIOLOGY

**Influence of Climate.**—Ordinarily, acute infections of the upper respiratory tract are less common and have fewer complications in the tropics than in colder climates. This is especially true in small islands in which the population is sparse and in which the inhabitants have relatively few contacts with the outside world. Thus it has been found by Milam and Smilie<sup>3</sup> that the incidence of colds among the natives of St. John, United States Virgin Islands, is less than one a year, but is greater than two a year among inhabitants of the United States. Since colds are notoriously less common during the summer months in the United States, it would appear at first glance that a warm climate is the most important deterrent of such infections. But it has been known for a long time that upper respiratory tract infections are less common in isolated arctic communities than more thickly populated temperate regions. For example, Paul and Freese<sup>4</sup> found that colds practically disappear during the winter months in Spitzbergen, but each spring, within forty-eight hours of the arrival of the first tourist steamer, an epidemic of colds breaks out among the inhabitants and continues during the summer months until nearly all have suffered from the disease. Even so, the yearly incidence among these people is only slightly greater than among the inhabitants of St. John and is definitely less than in the United States. It is also to be emphasized that the season for colds in Spitzbergen is the reverse of that in the United States. In

The opinions or assertions contained herein are the private ones of the writer and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

other words, the incidence of colds is the greatest at the time of year when contacts with the outside world are the greatest, although for the contacts themselves it is the season in which colds are at a minimum. On the other hand, *Cawston*<sup>5</sup> has found that epidemics of acute infectious diseases of the respiratory tract may assume alarming proportions in the tropics when populations are large and living conditions are crowded, such as in many areas of India and Africa. It is evident, therefore, that climate is not so important a factor in the epidemiology of such diseases as density of population and frequency of contacts with other communities.

No statistical studies of acute respiratory tract infections among the native and white populations of the tropical South Pacific islands have been found in the literature, but there is no reason to suppose that the incidence of these diseases is different from that in other islands in which surveys have been made. It is presumed, therefore, that common infections of temperate climates, such as colds, grippe and pneumonia, are infrequent. A number of civilian residents and white planters in different groups of islands were questioned about their personal experiences with these infections during peace time. It was generally agreed that colds and grippe were not of common occurrence but were usually more severe than in temperate zones. In fact, one man was so emphatic about the severity of colds that he dreaded a relapse of malaria much less than an attack of a common cold. Pneumonia however is rare. Although these are only opinions and are the observations of men not trained in medicine, they are believed to be accurate.

In the present war in the South Pacific all fighting has been in the tropics. However, many of our bases are located in the temperate areas of Australia and New Zealand in which respiratory tract diseases are much the same in incidence and severity as in the United States. Large bodies of men are frequently transported between the United States and these countries and between all of them and advanced bases and combat areas in the tropics. Furthermore, communication by air among all of these areas has for some time been extensive. It is not surprising therefore, that experiences aboard this hospital ship have shown these diseases to be relatively more frequent than might be expected.

In general, during the first two years after Pearl Harbor, the ship had two functions. One was to act as a highly mobile hospital for units of the fleet. For considerable periods the ship was stationed at advanced bases, usually in some isolated tropical island. At these times, patients were admitted from permanent neighboring shore facilities and from ships having had little recent contact with thickly populated areas in the temperate regions. It was possible, therefore, to form definite impressions about the incidence of respiratory tract infections in groups which were relatively stable so far as outside contacts are concerned.

The second function was the evacuation of casualties from advanced bases to shore hospitals usually situated in the temperate zone. These trips gave an opportunity to observe the members of the crew after exposure to urban communities where respiratory infections were prevalent.

**Common Cold**—Interest was first aroused in these infections when the ship was stationed at a tropical island before the arrival of land forces. At this time the crew was free of obvious colds and sore throat. The natives on the island likewise appeared to be free of these diseases. Upon the arrival of a large garrison from the United States, however, a mild epidemic of colds broke out almost immediately among the natives and before long among members of the ship's crew. From then on, colds were prevalent on the ship but were most frequent and in fact were anticipated after almost every trip to a port in the temperate zone. Although the morbidity rate was obviously high, no statistics were obtained because the great majority of men did not seek medical treatment and were not admitted to the sick list.

**Grippe**—The incidence of upper respiratory tract infections, more severe than the common cold, which are usually classified as grippe in the United States, was definitely less but was sufficiently great to cause considerable disability among the crew. According to the nomenclature in the Navy, infections characterized by mild fever, coryza, sore throat and cough in varying degrees are loosely grouped under the diagnosis of catarrhal fever. From the period July 1, 1942, to July 1, 1943, there were 9085 different admissions to the ship. Of these, 122 were cases of catarrhal fever. Seventy-two were members of the crew. Of these seventy-two, fifty were admitted immediately following trips to populous areas in the temperate zone. The twenty-two others probably acquired the infections through serial exposure to other members of the crew or to individuals coming from activities in more advanced bases. The fifty cases which were not among the ship's company originated in the tropics. It is not known just how prevalent catarrhal fever was on other ships and in shore establishments, since most activities were able to care for their own patients. There is every reason to suppose, however, that other ships had experiences similar to ours. It is also quite obvious that crews of ships and the large drafts of new men constantly arriving from the United States were an ever present source of infection for the more stable military populations of the advanced tropical bases, especially when resistance was lowered by prolonged segregation. Quite conceivably, outbreaks of these infections during times of combat might constitute a military problem. That this does not occur more often may be explained by the fact that before the attack assault troops ordinarily have trained either in the temperate zone or in areas where the military population is large. Previous exposure has therefore resulted in mass immunity.

**Diphtheria**—The occurrence of a number of cases of diphtheria, over a period of several months, during combat operations in the Solomons and near by islands shows, however, that even if troops have been regularly exposed to common infections of the respiratory tract before going into action, there is always the possibility of an epidemic. A case in point is the recent outbreak of "woodside throat" in South Australia which has been reported by Seymour.<sup>6</sup> At one time, 400 men out of 900 in one camp contracted the disease within one month. Fortunately, these were not concerned with military operations.

The occurrence of diphtheria in the present war in the Pacific is of considerable interest. The time of onset is not definitely known because the disease was not at first recognized until cases of postdiphtheritic paralysis began to occur. Consequently, it was some weeks before medical units in combat areas began to make smears and cultures in suspected cases. Eighteen cases were admitted to the ship of which thirteen had some manifestation of paralysis. One of these patients died of respiratory failure and acute myocarditis. Of the first fourteen cases in chronological sequence, all but one had paralytic phenomena. Of these thirteen cases, eight had received no antitoxin and five had received it a number of days after onset so that paralysis was not prevented. The last four cases admitted, however, had received adequate amounts of antitoxin within three days of onset and none of these developed paralysis.

In reviewing the history of these cases, it was quite apparent that the disease at onset was mild and was usually diagnosed as acute pharyngitis or tonsillitis, and specific treatment, if given at all, was too late to be effective. When medical personnel at advanced bases were aware that diphtheria was occurring, prompt laboratory diagnosis resulted in effective treatment and control.

It is not surprising that the disease was not immediately recognized. In the first place, diphtheria in the tropics is usually mild, although it is by no means uncommon. It is none the less dangerous because outbreaks can occur and considerable periods may elapse before recognition of the problem results in adequate control. Then the disease may be introduced by carriers into the temperate zones where its clinical severity may greatly increase. In the second place, the fighting at the time was under very adverse conditions. There was little opportunity for more than perfunctory examination of anything so apparently insignificant as a sore throat, when most activities were being harassed by enemy fire and when combat wounds took precedence over other illnesses. Furthermore, adequate facilities for the bacteriologic diagnosis of diphtheria were not at first available in the field.

The total number of cases also was not determined. First, not all cases of diphtheria were admitted to the ship, but there must have been many more than the eighteen which were examined. Second, in

all probability there were many cases undiagnosed in which the local manifestations in the nasopharynx were mild and in which postdiphtheritic paralysis did not occur in the absence of specific early treatment. Even in temperate climates, where the clinical course is more severe, only 10 per cent are said to develop these lesions. The actual number of infections, therefore, was probably much larger than those which were recognized. Another point in favor of this belief was the wide distribution of the known cases among different units. Of the eighteen, nine patients were marines, six were soldiers and three were sailors. The marines were from five different regiments and two other units. In two instances, marines were from the same regiment but not from the same company. Of the nine marines, six became ill on Island A, two on Island B, over 500 miles away, and one on Island C, 700 miles away from Island A. The six soldiers all became ill on Island A and were from the same regiment but were from five different units. The three sailors were from three different units, one at anchor in Island B. One of these was a hospital corpsman who had attended cases of diphtheria five weeks before. It is evident, therefore, that the disease over a period of several months was widely scattered among the armed forces in the area.

The origin of the disease is likewise in doubt. Since diphtheria is thought to be endemic in the tropics, the first cases may have been acquired from natives with whom the marines came in contact. After carriers were established among the troops, spread to the various units would be a natural result. More likely, however, was the presence of men among the armed forces who had acquired the carrier state in the temperate zone. Owing to the crowding and unsanitary conditions of combat, many others were infected or became carriers. It is probable, therefore, that a serious epidemic was averted by the fact that among the men the general average of immunity was high. Most of the enlisted men among the marines were under twenty-five years of age. Their childhood was sufficiently recent for many of them to have been artificially immunized, a practice which is now common in many communities of the United States. Our patients were questioned about previous inoculations for diphtheria but none of them remembered having been immunized. This omission may have been a factor in their susceptibility to the disease.

**Pneumonia**—At no time in the South Pacific were cases of pneumonia sufficiently numerous to be alarming. According to Bibb,<sup>7</sup> lobar pneumonia is only sporadic in Hawaii, and it is evidently not a problem in St. John.<sup>3</sup> Pneumonia is, therefore, uncommon in the tropics. During the one-year period mentioned, twenty-four patients were admitted to the ship with a diagnosis of pneumonia confirmed by clinical course and x-rays. Eight of these were well along in convalescence on admission. Sixteen were still ill enough for continuation of treatment. Seventeen cases were lobar and seven were lobular in distribution.

One of the latter was caused by the *Staphylococcus aureus*. Since most of the cases of lobar pneumonia were already receiving sulfonamides on admission, it is not surprising that in only one was a type-specific pneumococcus isolated on culture from the sputum. This was Type III. In fact, this was the only case in which a type-specific pneumococcus was isolated from the sputum or nasopharynx during the entire period, in spite of careful search in all cultures. However, the clinical course and x-ray findings in the other cases of lobar pneumonia suggest that they were of pneumococcic etiology. None of these, clinically, was suggestive of the severe virus pneumonia as it is known in the United States. However, two of the cases, classed with the group of lobular pneumonia, in which the sulfonamides were not given, had short, mild, febrile courses and lesions which on x-ray were confined to one lobe. It is possible, therefore, that some cases were caused by viruses or by bacteria other than pneumococci.

Since pneumococci were so uncommon in the nasopharynx during this period, it is natural that so few cases of lobar pneumonia occurred in a series of over 9000 admissions. It is interesting, therefore, to determine what contacts with carriers of pneumococci these patients may have had. If the case of staphylococcic pneumonia is excluded, four of the twenty-three remaining patients acquired their infections shortly after leaving the United States, five followed severe wounds or shipwreck, seven occurred on combat ships, five on shore stations in combat areas and three on shore stations in noncombat areas. Those who had just left the United States either harbored the pneumococcus themselves or were in close contact with others who did. From the histories it is not known how many of the remaining had recently left the United States, but it is to be repeated that in shore stations and on board ship new men still potential carriers of the pneumococcus were constantly arriving from the temperate zone. The susceptibility of many of these patients can readily be explained by the lowered resistance incident to fatigue, exposure, wounds or intercurrent disease.

**Acute Exacerbations of Chronic Infections.**—Acute exacerbations of chronic infections in the nasopharynx were more frequent than might be expected in a tropical climate. Thus, during the intervals when the ship was not evacuating casualties, one hundred and eight patients were admitted for tonsillectomy because of chronic tonsillitis and forty-three patients were admitted because of severe acute tonsillitis. Furthermore, eighteen cases of acute otitis media and thirty-seven cases of sinusitis were admitted to the ship. Previous colds and catarrhal fever, or lowered resistance due to the causes already enumerated, appear to have been precipitating factors in most instances. Because of recurrent disability, many of these patients were an actual hindrance to the service. Epidemiologically, these cases were important because they were potential sources of infection, especially in the crowded living quarters aboard ship.

## BACTERIOLOGY

**Basic Bacterial Flora of the Nasopharynx**—Statistical studies of the basic bacterial flora of the nasopharynx have shown differences in various parts of the world. During periods when respiratory tract infections are common, certain bacteria have been found in greater incidence than normal. There has been little proof in most instances, however, that these organisms are anything more than secondary invaders. Thus, Small<sup>8</sup> found that in Philadelphia, during the winter of 1921-1922, *Hemophilus influenzae* occurred in 71 per cent, pneumococci in 43 per cent and hemolytic streptococcus in 43 per cent of throat cultures. Eleven of these, however, had pneumonia. Shibley, Hanger and Dochez<sup>9</sup> found that, in a similar climate, the three most common organisms in the basic flora of the nasopharynx were, in order of frequency, gram-negative cocci, nonhemolytic streptococcus and *H. influenzae*. Transient organisms were *Staphylococcus albus*, hemolytic streptococcus, *Staph. aureus* and *citreus*, and pneumococcus. These organisms increased in numbers during the late stages of colds and were thought to be secondary invaders. Interestingly, pneumococci were found in only 0.5 per cent to 2.0 per cent of cultures. The basic flora was reported by Noble, Fisher and Brainard<sup>10</sup> to be *Streptococcus viridans* and gram-negative cocci, presumably of the *Neisseria* group. Other organisms were thought to be only transients although some of them became dominant during colds.

In a study of the bacterial flora among the Eskimos, Wells and Heinbecker<sup>11</sup> found, in order of frequency, *Streptococcus viridans*, diphtheria, diphtheroids, sarcinae, micrococci, indifferent streptococci and hemolytic streptococcus. During a year round study in Spitzbergen, gram-negative cocci, *Hemophilus influenzae*, indifferent streptococcus, hemolytic streptococcus, *Str. viridans*, intermediates and pneumococcus were found in order of frequency by Paul and Freese.<sup>4</sup>

In the tropical island of St. John, 40 per cent of all throats cultured by Milam and Smillie<sup>8</sup> showed pneumococci, which constituted 13 to 15 per cent of all organisms and which were strikingly constant during summer and winter, although in Alabama, pneumococci were almost entirely absent during normal periods. However, it was thought that the normal basic flora of St. John, Alabama and Labrador were essentially the same and consisted of gram-negative micrococci, *viridans* group, indifferent streptococcus and diphtheroids. During the recent epidemic of "woodside throat" in South Australia, Cooke, Atkinson, Mawson and Hurst<sup>12, 13</sup> found a comparable flora among controls but a very marked increase in *H. influenzae* in patients with the infection.

When the scope of the problem is considered, the recent literature is indeed scanty. It is to be concluded, therefore, that apparent variations in the bacterial flora can be ascribed to an insufficiency of data and to marked variations in the character of bacteria harbored by individuals from one period to another.

Although it is commonly accepted that when certain bacteria gain the ascendancy in flora of the nasopharynx during periods of respiratory infections, their role is only that of secondary invaders, some believe them to be of etiologic significance. Thus, Thomson and Thomson<sup>14</sup> are convinced that the pneumococcus, Hemophilus influenzae, streptococcus and Micrococcus catarrhalis are primary causes of colds. It seemed important to determine, therefore, what the basic bacterial flora was among the armed forces in the South Pacific and to what extent this flora was altered by attacks of respiratory disease.

**Bacterial Flora in the South Pacific Forces.**—During the period July 1, 1942 to July 1, 1943, 272 cultures were made from the nasopharynx. These represented 231 different cases. Of these cultures, 208 were of the throat, forty-five were of sputum, fifteen were of nose and four were of mouth. In all cases, the patients were suffering from some type of respiratory tract infection. More than half of them had chronic conditions such as bronchial asthma, lung abscess, pulmonary tuberculosis, chronic sinusitis or chronic tonsillitis. It is considered, therefore, that the basic bacterial flora of this group taken as a whole is representative of the period and the area. The accompanying table lists the total number of times each bacterium was isolated.

ORGANISMS ACCORDING TO THE NUMBER OF TIMES ISOLATED IN 272  
CULTURES

Staphylococcus albus	182
Nonhemolytic streptococcus	180
Alpha-hemolytic streptococcus	108
Beta-hemolytic streptococcus	77
Neisseria	58
Staphylococcus aureus	49
Diphtheroids	33
Hemophilus	14
Pneumococcus	7
Corynebacterium diphtheriae	1
Miscellaneous	9

It is apparent that Staphylococcus albus and nonhemolytic streptococcus are the most numerous and occur in equal numbers. Alpha-hemolytic streptococcus is only slightly less frequent. Therefore, these three bacteria are thought to constitute the basic flora. The remaining organisms by contrast are incidental. The results differ, therefore, from those previously quoted. The most likely explanation for this variation is that contacts are the most important factors in determining the bacterial flora and that these organisms may have been characteristic only of the period under discussion. At some other time, another group of organisms might be in the ascendancy.

Furthermore, there is no change in the relative incidence of any of the organisms when cases of catarrhal fever and pneumonia are



grouped separately. However, in cases of acute tonsillitis, beta-hemolytic streptococcus is definitely more common than in the group as a whole. This is the one organism, therefore, which is shown to have etiologic significance.

The rarity of the pneumococcus is especially striking. In only seven cultures was an organism isolated which had its morphologic and cultural characteristics and only one of these could be typed. In view of this fact and the low incidence of pneumonia in the tropics, the pneumococcus must be unable to survive for long periods in warm climates.

#### SUMMARY

1 In peacetime, the incidence of respiratory tract infections is lower in isolated tropical and arctic communities than in the more populous areas of the temperate zone. Segregation of the inhabitants is a more important factor in the low incidence than is climate.

2 The occurrence of upper respiratory tract infections among our armed forces in the tropical South Pacific is greater than the normal incidence in these latitudes. This is especially true of colds and catarrhal fever and is evidently due to the large influx of men from the temperate zone and to crowded living accommodations.

3 Diphtheria, although mild, is not uncommon in the tropics as illustrated by its occurrence in the armed forces during the campaign of the Solomon Islands.

4 Pneumonia is rare in the tropics and has not been an important medical problem in the war in the Pacific.

5 The basic bacterial flora of the nasopharynx differs greatly in widely separated communities, from time to time in the same community and at varying periods in the same individual. Segregation tends to make the flora more stable and intermingling of populations tends to make it more varied. Statistical data is insufficient, however, for a proper evaluation of the factors involved.

6 During the period July 1, 1942 to July 1, 1943, the basic bacterial flora in the armed forces in the South Pacific consisted of *Staphylococcus albus*, nonhemolytic streptococcus and alpha-hemolytic streptococcus. Other organisms were incidental or transitory in occurrence.

7 The beta-hemolytic streptococcus was frequently responsible for acute tonsillitis among service personnel. It was not demonstrated that common organisms of the nasopharynx were primary causes of colds and catarrhal fever.

8 The pneumococcus was strikingly rare. This organism is probably unable to survive for long periods in the tropics.

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# BENEFICIAL AND HARMFUL EFFECTS OF FLUORINE ON HUMAN TEETH

JOHN LANSBURY, M D , M S (MED ), F A C P \*

ALTHOUGH Gay Lussac found fluorine in dental enamel as long ago as 1805, the importance of this element to dental health has only recently been discovered. The reawakening of interest has come through recognition of fluorine as the offending agent in waters which cause "mottled enamel." As will be seen later, an excess of fluorine may be harmful, but on the other hand, a lack of fluorine may also be harmful by favoring the development of caries. These facts make the regulation of fluorine intake a matter for permanent concern to the guardians of public health.

## FLUORINE AND SOURCES

Fluorine is the heaviest of the four halogens, being preceded by chlorine, bromine and iodine in the periodic table. Because it lacks the ubiquity of the chloride radical in body-economy as well as the established pharmacologic value of bromides and iodides, its role as a normal constituent of body tissues has been rather neglected. Probably most of us remember fluorine mainly for its violent corrosive properties.

By far the most important source of fluorine is drinking water. The fluorine content varies from traces which can be barely detected, to concentrations of 7 or more milligrams per liter. Waters which are obtained from very deep sources are especially apt to be rich in fluorine.

Recent studies, though incomplete, suggest that foods are a less important source of fluorine. Vegetables grown in soils of varying fluorine content do not contain parallel amounts of fluorine,<sup>1</sup> although they may take up varying amounts of it from the water in which they are cooked. (Tea, processed foods and bone products are an exception since they contain relatively large amounts of fluorine, although still not enough to make up for a deficiency in the water supply.)

A rare source of fluorine is dust from mining and smelting operations involving the fluorine-containing mineral "cryolite." Exposed workers may ingest as much as 25 mg a day which, in a year or so, results in chronic fluorine poisoning. Fluorine is a constituent of certain roach powders, rat poisons and insecticide sprays, all of which may be an accidental source of acute fluorine poisoning in humans.

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From the Department of Medicine, Temple University, and the Temple University Hospital, Philadelphia

\* Associate Professor of Medicine, Temple University

The optimum intake of fluorine is probably about 1 mg per day, or a water supply containing about 0.9 parts per million.

### FLUORINE POISONING

Fluorides cause local necrosis when applied in concentrations of 2 per cent or more. The application or infiltration locally of calcium gluconate will arrest this escharotic action. In acute systemic poisoning, the parathyroid glands show degenerative changes. (The parathyroid hormone antagonizes the action of fluorine.) Excess fluorides interfere with several enzyme systems, the activity of ascorbic acid and the blood-clotting and phosphatase mechanisms.

Chronic fluorine poisoning in rats causes a peculiar rachitic-like stunting of the skeleton. In man a general osteosclerosis is produced after prolonged exposure to large quantities. In lesser amounts "mottled enamel" occurs under special circumstances, as will be seen later.

### PHYSIOLOGY OF FLUORINE

The studies of Machle and his co-workers<sup>2</sup> show that ingested fluorides are excreted 90 per cent in the urine. The excretion by bowel is fairly constant. Excessive perspiration may also be a source of appreciable excretion. A small amount is excreted in milk of the lactating animal. The average excretion in humans is 1 mg per day, and at the ordinary rate of ingestion little or no fluorine seems to be stored. When larger amounts are ingested, about half is stored and half excreted. When the increased ingestion is stopped, only normal amounts are excreted thus indicating that the stored portion remains fixed—presumably in the bones. It is possible to increase the fluorine content of bone to 100 times the normal amount (0.1 gm/kilo to 11 gm/kilo) without any change in the x-ray appearance, although there are changes in the bone in other respects. The approximate content of normal bone is 0.15 gm/per kilogram so that the average skeleton would by calculation contain 1.50 gm of fluorine. In 1914 Gautier<sup>3</sup> suggested that fluorine existed in the teeth in the chemical form of "apatite." The fluorapatite molecule is composed of calcium and phosphorous with a fluorine link. This idea has been furthered by McClendon in 1931,<sup>4</sup> who observed that dental enamel was harder than simple calcium phosphate. Later studies of the x-ray diffraction pattern confirms this view.

The fluoride excretion in cow's milk does not follow directly the amount digested, thus indicating a selective secretion by the mammary gland which protects the calf from excess. Similarly the milk teeth of babies show negligible degrees of mottling as compared with that of permanent teeth. This suggests a selective action on the part of the placenta which apparently permits only a fraction of the circulating fluorine to pass to the fetal bloodstream.

Although the deposition of fluorine in dental enamel is largely ac-

completed early in life when the permanent teeth are being formed, this is not the only way in which fluorine can reach the enamel. Careful studies on rats, and some clinical experiences in children, which will be discussed later, prove that fluorides coming in contact with the teeth are absorbed directly by the enamel. How important this direct absorption from drinking water is in human dentition has not been determined, but it seems to be only slight. In the mouth, fluorides reduce the lactobacillus content of the saliva. This action, however, is not believed to be of great importance in the prevention of caries. Salivary amylase, which may play a role in the production of caries, does not seem to be much affected by fluorides.

#### "MOTTLED ENAMEL"

"Mottled enamel" was first mentioned in the American literature in 1902 by Eager<sup>5</sup> of the U S Marines who reported the condition as endemic near Naples, Italy, and referred to an original description of the disease by Professor Stefano Chiaie. The first American cases were reported in the United States by McKay and Black in 1916.<sup>6</sup> McKay carried out a great many investigations over a long period of years on the subject, and arrived at the conclusion that the disease was due to some unidentified agent in drinking water. In 1931 Smith, Lantz and Smith<sup>7</sup> recognized the similarity between dental lesions previously known to be produced by feeding sodium fluoride to rats (McCollum et al<sup>8</sup>) and the lesions of mottled enamel in humans. In the same year Churchill<sup>9</sup> correlated his previous finding of high fluorine content in certain drinking waters with the incidence of mottled enamel. Since then many surveys of fluorine content of drinking water have been made. The disease "mottled enamel" (now referred to as *dental fluorosis*) has been found to be endemic in more than 400 communities in the United States and has also been recognized in various countries all over the world.

Only those who have been born and brought up in an endemic area or who have moved to such localities early in life are affected. The deciduous teeth are rarely affected. Mild cases show white chalky deposits in the permanent teeth, more severe cases show brownish discoloration which may be very unsightly. In very severe cases the teeth are poorly formed and inclined to be brittle. A survey in 1940 of St David's County, where almost everyone is affected,<sup>10</sup> showed that 50 per cent of the persons over twenty-four years had lost all their teeth.

The actual agent producing the brownish discoloration may be of organic origin since it can be removed by local application of hydrogen peroxide and ether. Permanent benefit by such treatment has been reported by Ames.<sup>11</sup> Naturally, the abnormal state of the tooth is not changed. Mottled enamel cannot be cured, and must therefore be dealt with by prevention. This has already been accomplished in certain

communities by changing the water supply to one of low fluorine content. (The amount of fluorine in water sufficient to cause fluorosis is 1.7 or more parts per million.) For those who are forced to live in communities where dangerous fluorine water levels obtain, the problem may be partly met by importing drinking water or by the use of bone ash filters which absorb fluorine from the water. As noted before, people whose permanent teeth have erupted are not affected by moving into an area where mottled enamel is endemic. Other than the dental changes already referred to, no other systemic effects have been noted, although it is quite possible that the quantity of fluorine ingested may be related to health in unsuspected ways.

#### FLUORINE AND DENTAL CARIES

One need hardly point out that dental caries is a prevalent disease, or that its prevention and cure is an unsolved medical problem. We know that it is in some way related to nutrition, calcium and phosphorus and to fat-soluble vitamins. Also such factors as salivary acidity, carbohydrate breakdown and local dental trauma all play a role. The Research Council of the American Dental Association recognizes these factors in the initiation of dental caries, but regards the process from there on as being the result of bacterial action.

While local dental care and diet probably help to reduce the incidence of dental caries, we are still faced with the fact that certain individuals who take little or no care of their teeth may be singularly free from caries, while others, who practice the recommended prophylactic measures, may suffer severe degrees of dental decay. These, and other facts, convince one that the ultimate cause of dental caries is unknown. Any factor, therefore, which might have a bearing on the subject is important. Such a factor is fluorine.

The earlier studies of McKay indicated a lower incidence of dental caries in those areas afflicted with mottled enamel. However, we have already noted a seemingly contrary finding in the St. David's survey by Smith and Smith<sup>10</sup> where almost 100 per cent of the population have severe mottled enamel and where the incidence of caries is high, and the ensuing destruction of the affected teeth unusually rapid. These seemingly conflicting observations were apparently due to difference in the degree of fluorosis.

Through subsequent epidemiologic surveys in which the incidence of dental caries in school children was correlated with the fluorine content of their drinking water, it has become apparent that a low fluorine intake is associated with a high incidence of dental caries. Striking evidence for this has come from surveys in nearby communities where climate and food, as well as general living conditions, are comparable, but where the water supply, coming from different sources, affords a gross difference of fluorine intake. A good example of such a study is that reported by Dean and associates in 1942<sup>12</sup> who

compared the incidence of dental caries in Maywood, Illinois, where the water supply contains 1.4 parts of fluorine per million, with that of a district 2 miles distant (Oak Park), where only traces of fluorine were identified in the drinking water. The incidence of caries in Oak Park was three times that of Maywood.

From these and other studies, Cox and Levin advance the theory that deficiency of fluorine intake during the early years of life results in a dental enamel which is soft and highly susceptible to caries. The enamel which contains the optimum amount of fluorine is highly resistant to caries. But the enamel which is laid down during the ingestion of excess fluorine is brittle, and the teeth succumb rapidly to caries, and incidentally of course show the tell-tale mottling.

Naturally these observations suggest that dental caries might be at least partly controlled by adding sufficient fluorine to the water supply. Arnold, Dean and Elvove in 1942<sup>13</sup> found no decrease in the incidence of caries in children and adolescents following an enrichment from 0.1 parts per million of fluorine to 0.7 parts per million of their drinking water over a two-year period. This apparently discouraging report is, I believe, misleading. The method fails to take into account the fact that the fluorine must be ingested in early infancy so that the enamel of the unerupted teeth can be properly formed. Since these teeth do not appear and become subject to caries for a period of six to ten years, the period of observation is too short to draw conclusions, and the ages of the children are too widely spread.

A controlled experiment lasting over a period of ten years will be necessary to confirm the value of adding fluorides to the water supply. Such an experiment is being undertaken by the New York Health Department using Newburgh, New York, as the experimental area with Kingston, New York, which is 23 miles distant, as the control. It is, I believe, reasonable to expect that, as mottled enamel has been made to disappear over a number of years by the change in water supply from an excessively high to a normal or low fluorine content,<sup>14</sup> so dental caries may be lessened by changing from a fluorine-poor water supply to one with optimum content of fluorine. The best result to be expected would be a 50 or 60 per cent reduction in the incidence of caries.

Although the prospects of preventing caries by public health programs which would enrich the water supply with fluorine are promising, the possible benefit of local application by fluorides must not be forgotten.

The known affinity of bone and enamel for fluorine, and the experimentally proved ability of dental enamel to take up fluorine from drinking water by direct absorption have led to a clinical trial of application of fluorides to teeth. Bibby<sup>15</sup> and Cheyne<sup>16</sup> independently in 1942 found that local application of 1 per cent or less fluoride to children's teeth resulted in a 50 per cent reduction of new caries over a

two-year period Knutson and Armstrong in 1943<sup>17</sup> treated 289 school children by application of 2 per cent sodium fluoride to the cleansed teeth on one side of the mouth. The untreated side of the mouth served as a control and, in addition, 326 children in which the teeth were only cleaned, were further controls. The fluoride solution was applied at weekly intervals over a period of eight to fifteen weeks. A year later, the incidence of fresh caries was 38 per cent less in the treated cases than in the untreated controls. Those teeth which were already carious were not affected by the fluoride application, and proceeded to develop the same additional number of carious areas as the controls. The optimum concentration of fluoride solution and the optimum interval and number of applications have yet to be worked out and may conceivably give better results. The possibility of arresting established caries by local treatment with fluorine has not yet been proved. In the experiment just referred to, the untreated side of the mouth showed the same incidence of fresh caries as the untreated controls. This would seem to indicate that the action of sodium fluoride was purely local and not due to any changes in the salivary enzymes.

#### CONCLUSION

The importance of the fluorine content in drinking water to dental health has been proved. The possibility of reducing the incidence of mottled enamel by substituting a water supply of low or optimum fluorine content has been proved. The possibility of reducing the incidence of dental caries by enriching drinking water with fluorine seems very probable but has not yet been proved, and will not be proved for at least ten years. The topical application of 2 per cent sodium fluoride to teeth seems to be a safe and a partly successful method of preventing dental caries. From present data, it would seem that the most that could be expected from either method would be a 50 per cent reduction in the incidence of caries. While this is an impressive and very worth-while result which justifies further research and effort, it cannot be regarded as the final answer to the problem. In fact, it promises to be almost exactly half the answer. In other words, some other factors, not as yet understood, are equally important in the causation of dental caries. The interest in the fluorine-dental relation should continue and should expand but it should not exclude an equal interest in researches into the cause of the other 50 per cent of dental caries.

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# FROM THE PENNSYLVANIA HOSPITAL OVERSEAS

## INTRODUCTION

THERE IS no lack of medical writings on war medicine. Some are enlightening and some are not. A desire to publish one's experiences in a new field may be difficult to suppress until it is matured by time and volume. One may be critical of the recording of immature ideas—a product of haste. On the other hand, the failure to share the results of observations which present the crystallization of experience by sheer time and numbers into something worthwhile is probably a more serious offense. Much information having a practical application has been collected and correlated. This may be presented, although elaboration on some of the most recent advances in the management of certain tropical diseases is restricted for military reasons.

Medical officers, new to the tropics, grope about for information on diseases with which they may have had little or no experience and which, from the military point of view, are inadequately dealt with in textbooks.

Members of the unit from which these papers emanate were no exception. The process of learning tropical medicine the "hard way" was facilitated, however, by medical colleagues from New Zealand and Australia. Opportunities to attend their conferences and visit their hospitals afforded a stimulating exchange of ideas from which all benefited. The staff members of an Australian general hospital, especially Major R. Grant, Major W. E. King, Captain G. C. McKechnie and Captain Moore, were very helpful. Officers of another general hospital of New Zealand also cooperated in every possible way. The experience of years in the practice of tropical medicine was repeatedly placed at our disposal by Lt. Colonel E. G. Sayres of the latter institution.

As originally planned, this group of papers included articles by the following authors which were completed but their publication has been delayed on the grounds of military security: Lt. Colonel Joseph B. Vander Veer, Captain Ian G. Hodge, Captain Leonard W. Parkhurst, Captain Eric Denhoff, Lt. Colonel Gladwyn Graham and Lt. Colonel John H. Gibbon, Jr. It is regretted that these articles could not be included in the number.

The disorders considered in this collection of papers are among the more common to be observed. They are dealt with in a manner calculated to be of greatest assistance to medical officers entering the tropics for the first time and to the physicians who will be called upon to treat many of these diseases in personnel returning from the fighting.

front They are presented by authors in an affiliated unit of a teaching institution which has served continuously since January of 1942—except when traveling from one assignment to another—in the South and Southwest Pacific Theaters.

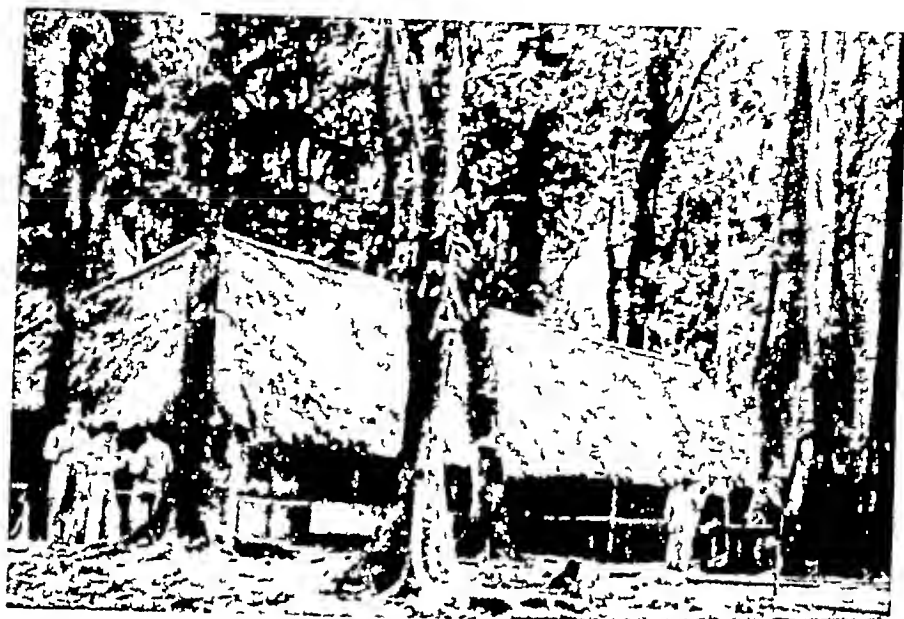


Fig 123 —Hospital ward in the jungle

A discussion of tropical diseases is timely To have these subjects presented in a practical manner by a group qualified as medical instructors and with ideas matured by the experience of being at grips with these problems for more than two and one-half years enhances inestimably the value of such a publication

COLONEL GARFIELD G DUNCAN  
MEDICAL CORPS, ARMY OF THE UNITED STATES

# PRACTICAL CONSIDERATIONS OF MALARIA

LT COLONEL JOSEPH B VANDER VEER AND  
CAPTAIN CARL A HEDBLOM, JR

MEDICAL CORPS ARMY OF THE UNITED STATES

MALARIA, the scourge of the armies in the Middle East in World War I, is the most important medical problem in the present conflict. This most widespread of all tropical diseases assumes new importance in wartime with the introduction of new strains of malaria parasites into endemic and hyperendemic areas and the return of chronic cases, infectious for the anopheline mosquito, to areas where the disease had previously been uncommon or absent.

In World War I, as many as 25 per cent of the personnel of the opposing armies were acutely ill with malaria a major portion of the time on the Italian, East African, Palestine, Macedonian and Mesopotamian theaters.<sup>1</sup> One army of nearly 150,000 troops was unable to put 20,000 well troops into combat at one period owing to the ravages of this disease. The success of many battles and even campaigns in this war may well depend on successful malaria control. In island and jungle warfare, where reinforcement may be difficult or impossible at times, malaria discipline and antimalaria supplies may be deciding factors.

The *Anopheles quadrimaculatus*, a suitable vector for the important malaria plasmodia, is found in many sectors of the United States. Rapid air transport may serve to bring infected mosquitoes and even more important, new species of anophelines, to our country. In a new location without their natural enemies they may multiply rapidly and be a vector for new or old strains of plasmodia. In Brazil in 1930 the *Anopheles gambiae* was accidentally introduced. An epidemic which cost the lives of 14,000 persons resulted despite the fact malaria was already present in this area. Unless public health measures are unusually efficient, many secondary cases and even severe epidemics must be expected in the United States. The general practitioner must become familiar with the ubiquitous, clinical manifestations of this disease, especially common in the primary attack. In the past decade many of the larger cities have had small outbreaks of severe, often fatal, malaria, in drug addicts, transmitted by hypodermic syringes. Larger and more frequent outbreaks of this nature may be expected in the future.

## IMMUNITY

Immunity to malaria is a well-known mechanism of its production is scant (*Plasmodium knowlesi*) in rhesus.

man (for the treatment of paresis) have recently thrown new light on this important field. Some immunity is acquired during the course of the infection if the attack is not interrupted by immediate treatment. This immunity may be highly specific for the strain of the species of the plasmodium concerned and fail to protect against heterologous strains and species.<sup>2</sup> However, the immunity is not always limited to one strain, considerable crossing to others having been observed. In addition, a great variation in the virulence and infectivity occurs in different strains of the same species of malaria parasites. It is well known that a high degree of immunity is nearly universal in the adult native population of hyperendemic areas, as the result of repeated infections in childhood. This immunity is ineffective, however, against new strains of malaria introduced into these areas. Children of immune parents show no innate immunity, which accounts for the high mortality rate in native infants and children. In artificially inoculated patients it has been found that complete homologous immunity may last for three years and some degree of immunity may remain after seven years.<sup>3</sup>

The frequent inability to induce *Plasmodium vivax* malaria in Negroes in the treatment for syphilis of the central nervous system led to the assumption that there was considerable racial immunity.<sup>4</sup> However, it is known that *vivax* malaria is induced without difficulty in Negroes who have spent all their lives in areas such as New York and Boston.

#### THE MALARIA PARASITE

There are four known species of human malaria plasmodia and each species has many strains. These vary in virulence, infectivity for mosquitoes and reaction to specific antimalaria therapy. Definite morphologic and physiologic differences are present in different strains of the same species. The important types are the *P. vivax*, the cause of benign tertian malaria and *P. falciparum*, the cause of malignant tertian or estivo-autumnal malaria. These two species are the relevant ones from the military and postwar standpoint. *P. malariae*, the etiologic factor in quartan malaria, is less important as this infection is infrequent in most of the malarious areas and is a rare cause of disability in soldiers. It does have a great tendency to relapse, however, often after many years of good health. *P. ovale*, the cause of mild tertian fever, is a rare cause of malaria in limited areas. The disease is a mild one and the parasites tend to die out spontaneously. Relapses are uncommon.

For a detailed description of the malaria parasites including the development of the asexual cycle in man and the sexual cycle in the mosquito, the reader is referred to the textbooks of tropical medicine. Proficiency in the laboratory diagnosis of malaria, on which the ultimate diagnosis of this disease rests, cannot be obtained from textbooks or charts but only from the careful study of thick and thin blood smears.

## PATHOLOGICAL PHYSIOLOGY

The varied clinical manifestations of malaria are explained by the bodily reactions to the plasmodium in its various stages of development, to the localization of the parasites in the spleen, liver and bone marrow and to the immunity of the host. The blocking of capillaries by parasitized red blood cells causes some of the severe manifestation of "pernicious" malaria, the name given to the severe forms of malignant tertian infection. *P. falciparum* is the most invasive of the parasites and, in the very severe cases, as many as one-half of the red blood cells may be attacked. The exact cause of the characteristic paroxysm of malaria is not known. It is undoubtedly related to the release of merozoites and the contents of the red blood cells, coincident with their rupture. The number of parasites formed in the red blood cells does not necessarily determine the severity of the clinical disease. In persons who have had repeated attacks of malaria the disease becomes less severe even though many parasites are present in the blood smears. Finally, in the adult native population of hyperendemic areas organisms are often found with no evidence of clinical malaria. In "suppressed" malaria in which the individual is infected with malaria but the clinical symptoms are held in abeyance by small repeated doses of antimalaria drugs, the plasmodia are often difficult to find and may show definite abnormalities in appearance.

## PATHOLOGICAL CHANGES

Malaria is seldom fatal when treatment is available except in the most severe forms of malignant tertian disease. On postmortem examination the main changes are seen in the spleen, liver, bone marrow and brain. In acute cases the spleen may be only slightly enlarged with swollen, soft splenic pulp. With long standing infections the splenomegaly is greater and may be extreme. The spleen itself is firm or hard in consistency and the cut surface has a slate-gray color as the result of diffuse pigmentation. Microscopic examination reveals extensive invasion by parasites and a diffuse pigmentation of the endothelial cells. These cells may also show plasmodia and fragments of red blood cells. The changes in the liver are the result of hyperplasia, congestion and degeneration. The cells of the reticulo-endothelial portions are filled with pigment and parasites. Enlargement, cloudy swelling and pigmentation are usually present grossly. The bone marrow is soft and dark red or reddish brown in color. The microscopic changes are similar to those seen in the spleen. In "cerebral" malaria, usually due to *P. falciparum*, the brain may have a grayish hue due to the extensive deposit of pigment. Masses of parasites and parasitized red blood cells may cause actual obstruction of capillaries. Hemorrhages may occur in the white matter.

Changes in the blood count in malaria are definite and often suggestive of this disease. Anemia of some degree is nearly invariable and

in recurrent and chronic malaria it may become marked. It is of secondary type. In malignant tertian malaria the much greater percentage of parasitized red blood cells makes a rapidly developing anemia more likely than in the other forms. Destruction of red blood cells by the asexual cycle of the parasite and hemolytic and toxic factors all play a part in the lowered red blood count and hemoglobin value. With recurrent and chronic malaria, poikilocytosis, anisocytosis and basophilic stippling are common. In blackwater fever, an acute, severe hemolytic anemia plays a large part in the general symptoms and fatal outcome of many of these cases. This disease occurs nearly entirely in the Caucasian race and in those who have resided in malarious areas for a considerable time. Recurrent or chronic malaria, usually of *P. falciparum* origin, is apparently the important factor. We have had no experience with this disease in Army personnel. The total leukocyte count during the acute paroxysm is usually normal or slightly elevated. This is especially true of the first attack of malaria. The polymorphonuclear cells and the nonfilamented ("stab") forms are often slightly increased at this time. In patients with regularly recurring paroxysms, a leukopenia is the rule just prior to the paroxysms and may occur between them. In our experience the total leukocyte count was relatively higher in the acute stages of the primary attacks of malaria than in the recurrent cases at the same stage. Counts of 8000 to 11,000 white blood cells were the rule in primary cases while counts of 4000 to 8000 were more common in the recurrent attacks. An actual increase in large mononuclear cells is common, especially in the chronic cases. Pigmentation of the leukocytes is a valuable and often nearly diagnostic feature in malaria. It is seldom present in significant amounts during the primary attack except in those patients in whom "suppressed" malaria has been present for some time before the clinical manifestations of the disease appear. In thick smears of such patients the brown malarial pigment is often prominent in the neutrophils. In chronic malaria, pigmentation of the leukocytes is a characteristic finding and next to finding the parasites is the most valuable diagnostic laboratory feature. It occurs especially in the large monocytes and neutrophils but may be found in all types of leukocytes.

#### CLINICAL MANIFESTATIONS

It is not the function of this paper to discuss in detail the classical, clinical pictures of the various types of malaria. For these the reader is referred to the textbooks of medicine. Our experience in the diagnosis and treatment of malaria prior to Army service consisted in the occasional case seen in sailors, returning vacationists, and, more rarely, drug addicts. Most of these were primary cases and they frequently presented a diagnostic problem. The truly protean nature of this disease, however, was not appreciated until we had the privilege of seeing a relatively large number of cases. We were fortunate in being in close

contact with the physicians of a New Zealand hospital, who had served in the Middle East earlier in the war. Their experience in diagnosis, treatment and laboratory technics was graciously conveyed to us at a time when we began to receive our first cases of malaria. Later, members of an Australian hospital, who had served in hyperendemic malarious areas both before and during the war, gave us valuable information on the nature of the disease as seen in areas we were about to enter. To all of these confreres we owe a debt of gratitude.

In most diseases the ultimate clinical picture depends on the type and virulence of the infective agent and the resistance, immunity and general condition of the host. Response to therapy, even when of a specific nature, may be most variable. All of these facts are exemplified repeatedly in malaria patients. It is doubtful if any other disease more frequently mimics important medical and surgical conditions. As a complicating disease appearing during the course of other illnesses, either as a recurrence of a previous attack of malaria or the development of clinical malaria from a suppressed state, it reigns supreme.

In uncomplicated, benign tertian and quartan malaria the clinical course is much more constant than in the malignant tertian (estivo-autumnal) type which may be most varied in its symptomatology. However, the primary attack of tertian malaria is frequently far from the common conception of regularly recurring paroxysms of chills, fever and sweats. Unless this is realized the diagnosis may go unsuspected for a considerable period or even be missed.

In latent or suppressed malaria there is no fever. At the onset of the clinical malaria, even with severe headache, nausea, vomiting and other symptoms, some patients have little or no fever. Any type of fever curve may be present. This is especially true in *P. falciparum* infections. In endemic malarious areas, obscure fevers of any variety should suggest the possibility of this disease. Chilliness is more common than true rigors in primary malaria. Rigors are the rule in recurrent *P. vivax* infections and may occur in relapses of *P. falciparum*. In quartan malaria, even though the number of parasitized red blood cells is much less than in benign or malignant tertian infection, the paroxysms are usually severe. When distinct paroxysms occur in malignant tertian malaria, they may be quotidian or tertian. More often the temperature curve is of a remittent type, often not unlike that seen in typhoid fever. The intermittent fevers of typical tertian and quartan malaria need no comment and are in themselves an aid in diagnosis.

The most frequent early symptoms of malaria are headache, malaise, anorexia and nausea and vomiting. Diarrhea is not uncommon. In some areas, gastro-intestinal symptoms with little or no fever are the presenting symptoms in nearly one-half of the cases.<sup>5</sup> An acute abdominal condition is frequently simulated especially by *P. falciparum* infections and routine preoperative smears should be taken in all emergency operative cases in malarious areas. An acute bronchitis may occur in



the early stages as a part of the disease, but there are seldom significant pulmonary signs on physical examination as the process is confined to the larger bronchi.

Herpes labialis is described as a common manifestation of benign tertian malaria, but has been infrequent in our experience. In benign tertian and quartan malaria, mental confusion is not uncommon at the height of the fever. True delirium is common in severe malignant tertian malaria and comatose states and convulsions may occur in the cerebral types of this disease.

The physical examination seldom shows any very significant findings. A rapidly enlarging spleen with fever is always suggestive of malaria. The spleen is frequently not palpable and seldom much enlarged in the primary attack. Tenderness on palpation is often evident even when this organ cannot be felt. With recurrent attacks the splenomegaly increases and the organ is firm and usually nontender. In some hyperendemic areas where *P. falciparum* and mixed *P. falciparum* and *P. vivax* infections are frequent, tenderness on palpation of the hepatic and splenic areas is present in nearly every case, even though enlargement of these organs cannot always be demonstrated.<sup>5</sup>

In Army practice in malarious areas, the disease is frequently modified and atypical in its manifestations because of prophylactic therapy. This prevents the development of the disease in many who are actually infected by parasites. This suppressed malaria remains symptomless until fatigue, exposure, other illness, injury, or similar factors cause the disease to break through.

Relapses are frequent in all of the common types of malaria. Quartan malaria has the greatest tendency to relapse. Late recurrences are a characteristic feature of benign tertian but not of the malignant tertian malaria. Most relapses occur within a few weeks to a few months after the initial attack. They tend to be milder and more readily controlled by therapy with each recurrence. Relapses frequently occur without apparent cause. More often they occur following fatigue, exposure, alcoholic excesses, intercurrent infections, fractures, operations, or other conditions which lower the bodily resistance. Relapses are uncommon when suppressive therapy is being carried out faithfully and medication is administered in adequate amounts. The inherent tendency of soldiers to avoid taking required medication must not be overlooked. Return of the disease after a two-year or more interval is usually the result of a reinfection although authentic cases of relapses of *P. malariae* (quartan) infections are reported occurring after an interval of several years. These usually have occurred following an obvious precipitating factor such as an injury or severe infection.

#### CASE REPORTS

The authors desire to present a number of case reports of patients who were suffering from various types and manifestations of malaria.

These cases illustrate a number of the important clinical features and diagnostic problems which may be encountered in this disease

CASE I.—A private, twenty-eight years of age was admitted to the hospital on January 15 1944. He had been in good health until three days before admission. During this period he had noted increasing frontal headache, generalized aches, and fever. He had had occasional weak and dizzy spells and increasing fatigue. Chilliness was frequent but he had no shaking chills. He stated that he thought he had the "grippe"

The patient had been in a malarious area for several weeks and he stated that he had taken atabrine (0.1 gm.) daily six times per week during that time.

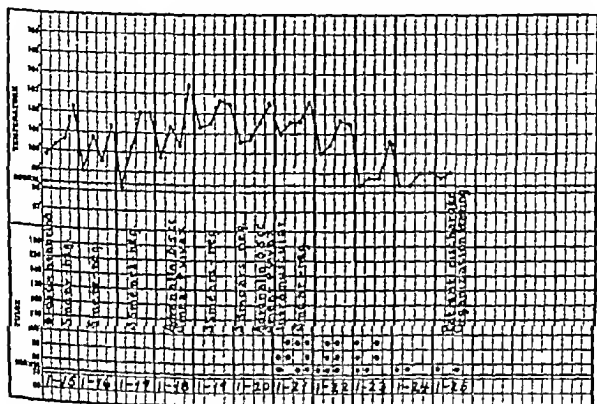


Fig. 124 (Case I) —Primary attack of benign, tertian (*P. vivax*) malaria. Note the remittent fever not uncommon in the initial attack, rather than the intermittent (tertian) type of temperature curve. Rapid clinical improvement occurred after atabrine therapy although the temperature responded more slowly. Malarial parasites were difficult to demonstrate in this patient and were found only after giving 0.5 cc. of adrenalin.

This suppressive dose of atabrine was discontinued at the time of hospitalization. There was no other significant history.

Physical examination showed an acutely ill male, who looked and felt miserable. He was apathetic and the tongue was coated. Neither herpes nor jaundice was present. The only positive finding was a tender palpable spleen, felt on deep inspiration.

During the first three days of hospitalization the patient had five negative smears for malarial parasites. Following the administration of 0.5 cc. of adrenalin (1:1000 solution) on the fourth hospital day a few plasmodia were demonstrated. The following day three negative smears were obtained at six hour intervals. The spleen could not be felt but there was tenderness on palpation of the splenic area and left flank. The temperature remained elevated and was of a

remittent type (Fig 124) The patient continued to have headache, malaise, anorexia and chilly sensations No frank chills occurred at any time and there was no vomiting On the evening of the sixth day, adrenalin was repeated and a smear taken one hour later was positive for *P vivax* (Three smears had previously been negative on this day) The plasmodia were still very infrequent.

Routine atabrine therapy (0.1 gm three times daily) was instituted (see Fig 126), supplemented by an initial dose of 0.2 gm atabrine dihydrochloride given intramuscularly Twenty-four hours later the patient felt and looked definitely better for the first time After forty-eight hours he appeared and felt nearly normal Thick blood smears revealed no malarial parasites on the first and second days after treatment was instituted The patient was discharged on the fifth day of therapy because his organization was leaving the area At the time of discharge he felt quite well, although his temperature was just becoming stabilized at a normal level

*Comment*—This patient illustrates the difficulties sometimes encountered in finding malaria parasites, even when repeated thick smears are employed This is especially true of cases in the primary attack of malaria If suppressive therapy has been given, as in this case, the problem is even more difficult This was stopped at the time of admission to the hospital Duplicate thick smears taken several times daily failed to reveal parasites until adrenalin was given The febrile course was of the remittent type, often present in the first attack, in contrast to the intermittent (tertian) fever nearly always encountered in relapses Clinical improvement and defervescence were rapid with atabrine therapy

CASE II—A private, twenty-five years of age, was hospitalized on September 28, 1943, because of chills, fever and headache He had been well until two days before admission when he developed a severe headache and a shaking chill followed by fever There was another chill before entrance to the hospital and the temperature was found to be 102.6° F shortly after he was sent to the ward A "dragging" pain was present in the upper abdomen but no vomiting had been present There were no genito-urinary symptoms The family history and past medical history were not relevant except that the patient had had four previous attacks of malaria with treatment for three of these in the combat area The last attack had been approximately two months before The patient stated that to his knowledge a positive smear for malaria parasites had never been obtained in the previous attacks

Physical examination revealed a well-developed, acutely ill male There were no significant findings in the head or neck except for injection of the throat The lungs were clear and the cardiac examination revealed no abnormal findings The pulse rate was 90 per minute and the blood pressure 115 systolic and 75 diastolic The abdomen was not distended but there was tenderness over the right upper quadrant on palpation and a slightly enlarged liver was demonstrable The spleen could not be palpated The genitalia, extremities, skin, and reflexes showed no abnormalities A clinical diagnosis of malaria, recurrent, due to *P vivax*, was made A smear for malaria parasites shortly after admission showed no plasmodia but many pigmented leukocytes A urinalysis gave normal values and findings Two smears the following day were negative and the patient

felt much improved and was fever free. On the morning of the third hospital day the temperature rose sharply to 101.8 F but there was no definite chill (see Fig 125). Two smears were taken on this day a few hours apart and the second was reported as showing *P. vivax*. Atabrine therapy was immediately started and the patient was given four doses of two tablets (0.1 gm. each) during the afternoon and evening of this day. There were headaches, malaise and some vomiting on this day although most of the medication was retained. The patient was given four tablets of atabrine daily for the next seven days. He felt considerably improved after the second day of treatment though the temperature

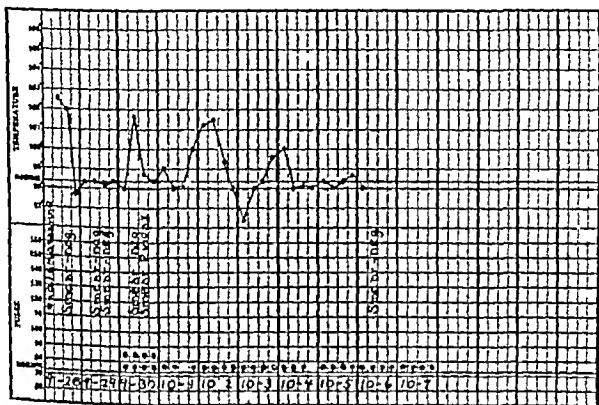


Fig 125 (Case II) —Relapsing malaria due to *P. vivax*, fifth attack. Note the intermittent type of fever with temperature elevation on the mornings of alternate days. Clinical improvement was rapid after treatment was begun. A more rapid reduction in fever would probably have occurred with the larger initial doses of atabrine now used during the first few days of therapy.

rose to 101.4 F and 100 F on the mornings of the fifth and seventh hospital days respectively. The patient was discharged to duty feeling quite well on the ninth hospital day. A smear for malaria parasites was negative on this day. He was instructed to take four atabrine tablets on the day of discharge and on the following day and after this to continue with the regular suppressive dose of six tablets per week.

**Comment**—This case illustrates typical recurrent malaria due to *P. vivax* occurring in a young person in good health. The attack was ushered in suddenly with headache, chill and fever but it was not very severe and specific therapy was withheld until the diagnosis was confirmed by finding the parasites. Finding the plasmodia in this type of case is usually not difficult if the patient has not been on suppressive or other therapy and if thick smear techniques are used. An enlarged,

firm spleen is common in the patients with recurrent attacks but it was not found in this case. Clinical improvement was rapid. Lesser rises in fever occurred forty-eight and ninety-six hours after therapy was begun. Larger doses of atabrine would probably have eliminated the fever more rapidly.

CASE III—A private, twenty-one years of age, was admitted to the hospital on September 10, 1943, complaining of severe generalized aching, fever and weakness. He was well until three days before admission when he became weak and felt as though he "had the flu." His eyes and head ached continually and he had fever and chilly sensations at night. There was no history of a frank chill. He had been unable to eat for two days, had taken very little water, but had not vomited. There were no cardiac, respiratory, or genito-urinary symptoms. The patient was born in Alabama and had had smallpox, diphtheria, typhoid fever, measles and malaria in childhood. His normal weight for the past year had been 125 pounds. The family history was noncontributory.

Physical examination revealed a fairly well-developed thin white male acutely ill with evidence of dehydration and fever. The pulse rate was 120 per minute. The eyes, ears, nose and throat were normal except for evidence of mild upper respiratory infection. The tongue was coated and dry. The heart and lungs were normal. The spleen was moderately enlarged and tender. There was no abnormality of the genitalia, reflexes, lymph nodes, or extremities. The skin was flushed, hot and dry and there were several infected insect bites on each ankle with small areas of surrounding cellulitis. The temperature on admission was 101.2° F. Later, on the first hospital day, the patient's temperature rose to 102.8° F. He was given 1000 cc of 5 per cent glucose intravenously as he was unable to take fluids by mouth. Atabrine and quinine were withheld pending result of the malaria smear. On the second day his temperature was 103° F and in spite of a negative malaria smear he was given six atabrine tablets 0.1 gm each. On the third hospital day his blood was found to contain *P. falciparum* and he was again given six tablets of atabrine. On the next two days he received a similar dose of atabrine with no perceptible change in his clinical condition. His temperature was 99° to 100° F each morning but rose to 103° or 104° F in the evening. He continued to complain of aching and general discomfort.

The infections on his legs responded to hot moist dressings and did not appear severe enough to be contributing to the fever. On the sixth hospital day the antimalaria therapy was changed to 0.6 gm (10 gr) of quinine sulfate three times a day. The following day a negative malaria smear was obtained but the patient was clinically unimproved. On the eighth hospital day he was given 0.6 gm (10 gr) of quinine dihydrochloride intravenously in 1000 cc of 5 per cent glucose in normal saline solution. In addition, 1.2 gm (20 gr) of quinine sulfate were taken by mouth. On each of the following three days he received 0.6 gm (10 gr) of quinine dihydrochloride intramuscularly and 1.2 gm (20 gr) of quinine sulfate by mouth with only slight clinical improvement. On the thirteenth hospital day a blood smear again showed malaria parasites but they were definitely *P. vivax*. On this day the patient was given 3.0 gm (45 gr) of quinine sulfate by mouth. This dose was repeated on three successive days and was coincident with a drop in temperature to normal (see Fig 126). The dosage of quinine was gradually decreased. The temperature remained down, and the patient showed rapid clinical improvement.

On admission the blood count revealed 75 per cent hemoglobin 4,510,000 red blood cells, and 7500 white blood cells. A differential count showed 61 neutro-

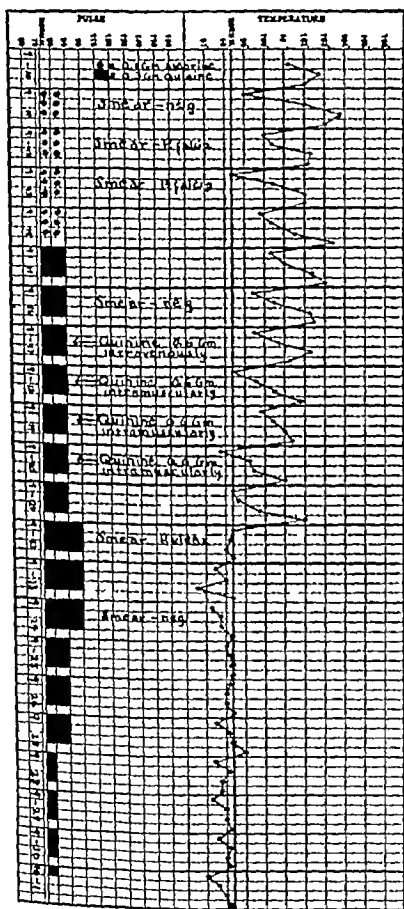


Fig 126 (Case III) - Primary attack of malaria with mixed infection by *P. falciparum* and *P. vivax*. Treatment was begun within twenty four hours after hospital admission but there was no clinical improvement or significant reduction in temperature for eleven days. This was despite the fact a great deal of therapy was given, including parenteral quinine. The failure to respond to treatment was probably the result of the mixed infection and inherently poor resistance in this patient. Inadequate blood levels of atabrine and quinine (given orally) may have been a factor in the poor response

phils, 30 lymphocytes, 4 monocytes, 2 eosinophils and 3 stab forms. Several urinalyses during the acute stage of the illness showed no abnormalities. Routine stool examination also showed no abnormalities.

On September 24, a smear for malaria parasites was negative (fifteenth hospital day) The patient's appetite improved but he failed to gain weight (he had dropped to 114 pounds) The spleen was still palpable but not tender On October 5, the patient was placed on suppressive therapy of one atabrine tablet daily Because of malnutrition the patient was kept in the hospital A high caloric diet, vitamins and iron were prescribed There was no fever and the patient felt well during the next several days However, on October 18, a malaria smear again showed *P vivax* in considerable numbers including sexual forms The next six days the patient received a total of twenty-six tablets of atabrine, and this was followed by five days of quinine medication, 2 gm (30 gr) per day The final three days he was given plasmochin, 0.01 gm., three times a day, in addition to the quinine On November 1, a smear for malaria parasites was negative and a urinalysis gave normal findings A blood count revealed 4,350,000 red blood cells and 70 per cent hemoglobin The patient was discharged to duty on November 3, 1943, feeling quite well

*Comment*—This case illustrates a failure of response to specific therapy given in the usual way The patient was severely ill on admission and after several days of atabrine-quinine therapy it was felt that probably some complicating disease or condition was responsible for the failure to improve It was thought, however, that the main underlying condition was malignant tertian (estivo-autumnal) malaria Quinine was given parenterally for several days, in addition to the oral dosage, so that we could be certain the drug was being absorbed Improvement came following this change in therapy The finding of the parasites of benign tertian malaria *P vivax* on the thirteenth hospital day probably explains the failure to respond to the usual therapy, on the basis of a mixed infection The presence of a positive smear for *P vivax* after a great deal of antimalaria therapy demonstrates the resistance this organism may have to treatment The personal factor may also be an important one and this patient no doubt represents the type who has little natural resistance to the malaria parasite and is prone to have repeated relapses It is an interesting commentary that the laboratory officer, knowing nothing regarding the treatment of the patient, made the remark that in the blood smear revealing *P vivax* the organisms were unusually numerous and well formed They resembled those seen in untreated cases of malaria At this time the patient had received a complete course of atabrine and was getting full doses of quinine This anomaly may be a manifestation of the underlying factors which caused the patient to respond so poorly to treatment

It is possible that the blood levels of atabrine and quinine were inadequate for the first ten days of treatment but this seems unlikely in view of the fact there was no vomiting or diarrhea and some of the therapy was given parenterally At present we are using larger doses of atabrine than were utilized in this patient but the quinine dosage was that regarded as adequate In mixed infections of this type, which are not infrequent in hyperendemic areas, the manifestations of the

malignant tertian parasite (*P. falciparum*) usually predominate over the benign tertian (*P. vivax*) during the acute phase of the disease. With relapses the benign tertian parasites and their manifestations usually assume the primary role

CASE IV—A private, an infantryman, twenty three years of age, was hospitalized on Christmas day 1943 because of headache and backache of five days' duration. One week before he had gone on special outpost duty, which was more strenuous than his previous routine. After two days, he noted bitemporal headache and generalized backache. His appetite disappeared and he was nauseated. No diarrhea was present. Four days before admission his temperature was

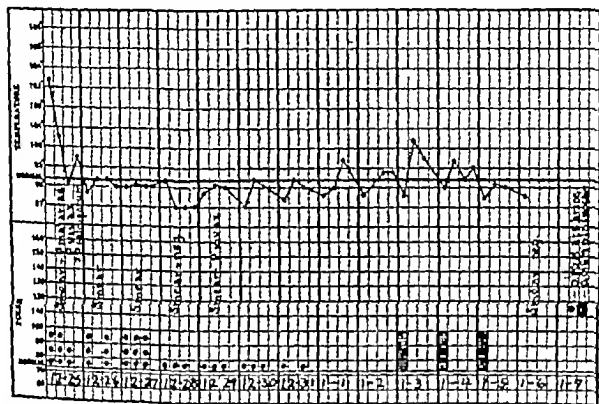


Fig 127 (Case IV)—Mixed infection with *P. vivax* and *P. malariae*. Fifth attack of malaria. Large numbers of plasmodia were present in the smears although the patient was only slightly ill clinically. A severe chill occurred on the morning of admission to the hospital. Note the rapid response of the temperature to routine atabrine (oral) therapy.

found to be 104 F., and he was put on a quarters status. He was given "white pills" and after no improvement was brought some distance to the hospital. A severe chill occurred on the morning of admission. On reaching the hospital his temperature was 103.4 F.

The past medical history revealed the patient was in a combat zone where malaria was hyperendemic for the first six months of 1943. In March he developed his first attack of malaria, which began with abdominal pain and diarrhea. He was quite ill, but was treated in his quarters for ten days (type of treatment not known). Four weeks later the disease recurred and was characterized by chills, fever, sweats and malaise every other day. He was again treated for ten days, both atabrine and quinine being administered. In mid June, a third attack of malaria occurred and in August, the fourth attack. The two latter



attacks were less severe and responded more quickly to treatment. Each occurred at a different location from the first attacks, but were considered relapses of the original infection. Between attacks, the patient had taken six atabrine tablets (0.1 gm each) weekly.

The family history revealed that his mother had died of cancer at the age of forty-five. The past medical history except for malaria was of no significance.

Physical examination after admission to the hospital revealed a moderately ill soldier, feverish, and uncomfortable from headache and back pains. There were no significant findings on general examination, except for an enlarged, tender spleen. This reached 4 cm below the left costal margin on deep inspiration and was quite firm. The liver was not enlarged or tender.

A clinical diagnosis of recurrent malaria, probably tertian, was made and therapy begun at once. (Three tablets of atabrine were given after each meal for the first three days.) By evening of the first day the temperature had fallen to normal and it showed no significant elevation thereafter. The patient stated that he felt fine and fit for duty twenty-four hours after admission. He was given routine atabrine antimalaria therapy for seven days, followed by no medication for two days and then plasmochin (0.01 gm) three times daily, after meals (Fig 127).

On admission to the ward (10 A.M.), a thick blood smear was taken. This smear was loaded with plasmodia, from 25 to 50 parasites per oil immersion field being present. Gametocytes and trophozoites of *P. malariae*, and late trophozoites of *P. vivax* were easily identified in this smear. It was thought the ring forms of *P. falciparum* might also be present. Thick and thin blood smears were taken at 4, 7, and 10 P.M. of this day. The same forms of *P. malariae* and *P. vivax* were found on all examinations, but the presence of *P. falciparum* organisms was not confirmed. The following day (December 26), smears were taken at 8 A.M. and 4, 7, and 10 P.M. No *P. malariae* trophozoites were found, but all forms of *P. vivax* persisted, on the first specimen. There was a definite decrease in the number of organisms during the day and only a few asexual forms of *P. vivax* were present on the 10 P.M. smear. A smear taken at 8 A.M., December 27, showed only a very few young trophozoites of *P. vivax* and one gametocyte of *P. malariae*. On two other smears on this day and three smears on December 28, no malaria parasites were found with thick smear techniques.

*Comment*—This case of malaria, with a mixed infection of *P. vivax* and *P. malariae*, demonstrates the great tendency of these types of malaria to relapse even when suppressive therapy is being followed. The clinical course of the disease was milder and the therapy more rapidly effective with successive attacks. The relatively mild nature of the fifth attack of malaria, which was associated with a massive infection of the blood stream, demonstrates the immunity and resistance which develop with repeated attacks with the same strain of organisms. Had the patient developed a new malaria infection with another strain of *P. vivax* or a different group of parasites, he would probably have been more ill. The rapid clinical response and decrease in parasitemia with adequate atabrine therapy illustrate the fact that little tolerance to this drug is built up with repeated therapy over a short period or with suppressive therapy.

**CASE V.**—A private, age twenty-one, was admitted to the hospital on December 14, 1943, after an illness of two days. He complained of general malaise, mild, persistent frontal headache, loss of appetite, fever and shaking chills. He stated that existing circumstances had made him extremely fatigued and that he had eaten irregularly and had not had enough sleep during the past several days. He also volunteered the information that he believed that he had malaria as he had developed malaria on five previous occasions under similar circumstances.

His account of his previous attacks of malaria was significant in this one respect, i.e., he had persuaded his medical officer that he was unable to tolerate atabrine because of diarrhea and therefore was allowed to take quinine, 0.3 gm. (5 grains), daily as a prophylactic dose. However he had been extremely negli-



Fig 128 (Case V)—Recurrent benign tertian malaria, sixth attack. A great many *P. vivax* parasites demonstrable including gametocytes. The clinical response to atabrine therapy was very rapid. Note the fact that despite a temperature of 103° F a few hours after starting treatment, no significant fever occurred after the first day of therapy. Full mixed-type therapy was utilized in this patient because of the large number of gametocytes present.

gent in taking his daily suppressive dose, the administration of which in his case was not supervised. He admitted that he believed that if he developed malaria frequently enough, he would be evacuated from the combat area. His previous attacks of malaria were uncomplicated and had required roughly a total of eight weeks hospitalization.

Physical examination revealed no abnormality except for the fact that the patient felt feverish. Despite an elevation of temperature to 103° F he did not appear particularly ill. The spleen and liver were not palpable.

The first smear taken on December 14, 1943, showed numerous *P. vivax* and gametocytes were easily found.

Routine atabrine therapy—0.9 gm. daily for the first three days followed by

0.3 gm daily for four days—was begun on the day after admission, December 15, 1943, and finished on December 21, 1943. The febrile response was excellent for the patient's temperature remained normal after the second day (see Fig 128). The patient continued to feel well and it was demonstrated to him that he could take atabrine without difficulty even in therapeutic doses.

Following the course of atabrine therapy he was given quinine—0.6 gm (10 grains)—three times daily for four days, accompanied by plasmochin—0.01 gm ( $\frac{1}{10}$  grain)—the last three days.

Smears taken after the therapy was completed were negative for malarial parasites and the patient was discharged, well, on December 28, 1943. He was instructed to take atabrine as a suppressive agent rather than quinine.

*Comment*—This patient with recurrent benign tertian malaria, sixth attack, had been in several different malarious areas during a twelve-months' period. It seems likely, however, that all of the attacks were manifestations of the original infection, acquired in Panama. The attacks followed exposure or fatigue. The patient had been allowed to take quinine—0.32 gm (5 grains)—daily as a suppressive therapy, rather than atabrine as he complained the latter drug gave him diarrhea. He had been excused from the atabrine muster for this reason and admitted he had not taken the suppressive therapy faithfully. Furthermore, it would be inadequate in the amounts supposed to be taken.

Despite large numbers of *P. vivax* parasites, including gametocytes, being demonstrable in the blood smears, the patient was only slightly ill. This was probably owing to acquired immunity to the strain of plasmodium with which he was infected. The response to full doses of atabrine therapy was immediate. Except for a temperature rise a few hours after treatment was begun there was no further elevation. After completion of a full course of atabrine (with no gastro-intestinal symptoms whatever) he was given full doses of quinine and plasmochin in an attempt to render him noninfectious.

**CASE VI\***—A marine captain, about twenty-eight years of age, was hospitalized on October 15, 1942. He had taken ill in the combat area three days prior to this and it was thought advisable to evacuate him by air to a rear base. At a stop enroute it was noted that his condition was worse and that his temperature was greatly elevated. He was sent at once to a nearby hospital.

On admission the temperature was 105.4° F, the pulse rate 120 and the respirations 40. No history could be obtained from the patient as he was delirious and disoriented as to time and place. The skin was hot, dry and flushed, the conjunctivae were injected and the pharynx was reddened. The heart was normal except for the tachycardia. Examination of the lungs revealed slight dullness at the base of the right lower lobe posteriorly and fine and coarse rales at both bases, more on the right. The abdomen was distended. Enlargement of the liver or spleen could not be demonstrated. The tendon reflexes were absent. A Babinski reflex was not present.

Blood examination showed a white count of 2000 cells per cu mm (differen-

\* We are indebted to Major E. E. Strobino, Chief of Medical Service, 109th Station Hospital for permission to use the data reported in Case VI.

nal count was not recorded) and a profusion of small ring forms of *P. falciparum*. No gametocytes were seen. Thin smears showed approximately 1 per cent of the red blood cells were parasitized.

The patient was placed immediately on parenteral quinine therapy because of the cerebral manifestations and vomiting. Unfortunately no record of the dosage of quinine was recorded. Intravenous fluids were given. For the first few days the patient's condition was extremely precarious. He continued to be delirious and at times was greatly agitated. Dysarthria, aphasia and dysphagia developed. Cranial nerve palsies of the sixth and seventh nerves became evident. Subconjunctival hemorrhages occurred.

During the first forty-eight hours the temperature fluctuated between 103 and 106° F. The pulse rate remained at 120 per minute and the respirations varied from 35 to 50 per minute. There was a gradual drop in the temperature, pulse and respirations beginning the third hospital day and reaching normal on the eighth day.

On the morning of the sixth hospital day the patient was dramatically improved. He noted he was in a hospital for the first time and became oriented and desired food. During the next few days he continued to improve and the cranial nerve signs disappeared. His speech improved but there was still an appreciable bulbar type of speech at the end of convalescence.

An x-ray of the lungs showed no abnormality the day after admission to the hospital. Urinalysis showed 3 plus albumin on three occasions but this gradually disappeared as the patient improved. On the sixth hospital day a blood count revealed hemoglobin, 70 per cent, red blood cells, 3,280,000, white blood cells, 14,000 with a differential count of 71 per cent polymorphonuclears, 25 per cent lymphocytes and 4 per cent monocytes. The nonprotein nitrogen was 50 mg per 100 cc. on this date.

*Comment*—Cerebral malaria, practically always the result of a *P. falciparum* infection, may be evidenced by protean manifestations. In this patient it was ushered in by high fever and delirium. This was soon followed by dysarthria, aphasia, dysphagia and cranial nerve palsies. The prognosis was in doubt for a period of nearly a week despite parenteral therapy. Some residual brain damage probably resulted. A marked febrile albuminuria occurred during the acute phase of the disease. A moderate anemia developed and the nonprotein nitrogen was elevated even after clinical improvement was evident. After recovery the patient volunteered the information that he had failed to take any suppressive therapy.

#### DIAGNOSIS

In endemic malarious areas any undiagnosed condition, febrile or nonfebrile, should be considered as possibly malaria. The diagnosis of relapse cases is seldom in doubt as the clinical course is more typical and the patient himself is often quite certain of the character of his illness. With pernicious malaria (nearly always due to *P. falciparum*) the diagnosis may be difficult. It is fortunate that such forms occur but rarely in those who are taking suppressive therapy. *P. falciparum*

malaria may have prodromal symptoms of only fever, headache and fatigue and yet coma or medical shock develop in a relatively short time. Cerebral malaria may be manifested by symptoms suggesting acute alcoholism or by convulsions. In severe cerebral malaria the temperature may be normal or even sub-normal with coma.<sup>6</sup>

There are few physical signs which aid in the clinical diagnosis of malaria. Herpes is not uncommon, the other conditions in which it is frequent being pneumonia, epidemic meningitis and common colds. Neither of these latter diseases are apt to be confused with malaria. A rapidly enlarging tender spleen in an acute case or a large firm spleen in a chronic case is suggestive of malaria. Tenderness over both the hepatic and splenic areas is not uncommon in severely ill patients. This is usually associated with vomiting. The temperature chart may be of value in suggesting the diagnosis. Tertian and quartan fevers are found only in malaria. Quotidian (daily) periodicity is, of course, found in association with many diseases. Combined infections with *P. falciparum* and *P. vivax* are not uncommon in some hyperendemic areas. In these patients the malignant tertian (*P. falciparum*) infection predominates over the benign tertian, from both the clinical and laboratory standpoints, in the acute phase. With relapses, the *P. vivax* infection is usually the predominant one.

**Differential Diagnosis.**—A great variety of diseases and conditions may be simulated by malaria. Among the most important are acute abdominal emergencies, acute appendicitis, acute gall bladder disease, obstructive conditions and dysentery. In endemic areas, malaria must always be considered with such a diagnosis and thick blood smears taken routinely, prior to operation. To complicate matters further, a positive blood smear may be obtained in patients whose primary condition is an acute abdominal one, the result of lowering of resistance in a person who has suppressed or latent malaria. In these patients, clinical judgment must decide the relative importance of the two conditions. Treatment of the malaria should, of course, be carried out even if operation is necessary.

Many tropical diseases are easily mistaken for malaria at various stages of their course.<sup>7</sup> Liver abscess (amebic), kala-azar, Malta fever, filariasis, trypanosomiasis, leprosy, relapsing fever and yellow fever should be mentioned. The diseases in temperate climates important to differentiate, include tuberculosis, malignant endocarditis, typhoid fever, *Brucella abortus* infections, pyelitis, perinephric abscess, liver abscess and subdiaphragmatic abscess.

Malaria should be thought of as a complicating disease in individuals who have had the disease in the past, in those who have recently come from malarious areas, or in those receiving suppressive therapy. A rise in temperature above that anticipated with the primary disease or a continuation of fever, not explained by infection, in association with either medical or surgical conditions should arouse suspicion. We have

seen malaria as a complicating factor in upper respiratory infections, pneumonia, primary atypical pneumonia, tonsillitis, severe dermatological conditions, acute appendicitis, gallbladder disease, postoperatively, and following fractures and wounds. The possibility of malaria developing in a recipient after transfusion should be borne in mind in areas where the donor is apt to have suppressed or latent malaria.

**Laboratory Diagnosis**—In any disease in which the etiologic agent is demonstrable by ordinary laboratory technics it is always desirable to confirm the clinical diagnosis by finding the causative organism. In areas where malaria is infrequent, more cases probably escape detection because the diagnosis is unsuspected and the parasites are not looked for, than because of failure to demonstrate the plasmodium. The important fact remains, however, that in an occasional patient gravely ill with clinical malaria, the parasites may not be demonstrable by good laboratory technics. Having a specific, effective therapy available for this disease, one is not justified in withholding treatment in such patients if the parasites cannot be demonstrated within a reasonable time. In patients with clinical malaria in which laboratory studies are negative or not available, a therapeutic test with an antimalarial drug may aid in the diagnosis. A rapid lowering of the temperature with clinical improvement in a febrile patient suspected of this disease is strong evidence that the clinical diagnosis of malaria is correct.

The utilization of thick blood smears, in which a relatively large amount of blood can be examined in a short period of time, is always desirable. The time of taking the smears is of equal importance. Smears should be obtained at intervals of four to six hours without regard to the time or type of fever. Results by this method are far superior to the custom often followed of taking smears in relation to the expected paroxysms.

Previous (immediate) suppressive therapy with atabrine or quinine makes demonstration of malarial parasites much more difficult as they are less frequent and are altered in appearance. Whenever practical we have discontinued suppressive therapy on patients hospitalized with possible malaria. Repeated smears are taken on these patients to establish the diagnosis. If the condition is not malaria, usually it is obvious after two or three days, and if malaria, a positive smear can usually be obtained by this time. Undiagnosed fevers (probably of virus origin) were frequent among the troops and many of these closely resembled primary malaria (the symptoms being headache, malaise, general aches, chilliness and fever). Nearly all these patients responded to rest and symptomatic therapy within two or three days. If patients recover quickly and completely without specific treatment and while off suppressive therapy, it is nearly certain that they did not have malaria. If specific therapy is started in such patients recovery progresses in the same manner but the positive diagnosis of malaria remains always in doubt. By means of thick smears taken repeatedly at intervals of four

to six hours by an experienced person, the diagnosis of malaria can be confirmed by finding the plasmodium in nearly all cases. Finding the plasmodia in primary cases is usually more difficult than in relapse cases, despite the fact the latter patients are less ill. In occasional patients, severely ill with pernicious (malignant tertian) malaria, parasites may not be demonstrable. Effective therapy should never be delayed in these patients, pending an exact laboratory diagnosis. Parenteral therapy may be life-saving in such cases and if the diagnosis should be incorrect no harm is done.

The use of epinephrine hydrochloride (adrenalin), 0.5 to 1.0 cc., hypodermically, to aid in obtaining a positive blood smear, is well known. Smears should be taken at one-half hour intervals for two or three hours after the injection. This procedure is of most value in acutely ill patients who have received no specific therapy. In chronic malaria, bone marrow biopsy may reveal the parasites when other methods fail.

False positive Kahn and Wassermann tests may be obtained from the serum of malaria patients during the acute disease and for a variable time after the attack. A great deal of research has been done on serological tests for the diagnosis of malaria during the past few years but none of these are as yet in a practical state for the diagnosis of the individual case.

### PROGNOSIS

One of the most characteristic features of malaria is its tendency to relapse. This is greatest in quartan, slightly less in vivax, and least in falciparum malaria. The relapse rate is considered as high as 65, 55 and 45 per cent respectively, by some authors. Quartan and tertian malaria are practically never fatal if adequate treatment is instituted early. Falciparum malaria may be fatal in the first attack and when cerebral or algid manifestations develop in this type the mortality may be 25 per cent or above. However, with prompt and efficient treatment a fatal outcome is extremely rare. Fortunately these manifestations seldom occur in those taking suppressive therapy. The over-all mortality varies considerably in various areas. In temperate climates with average living conditions it is under 1 per cent. In tropical countries and in primitive peoples it may be as high as 10 per cent.

### SUMMARY

1. Malaria is the most important medical problem of the war. In the postwar era it may represent a serious problem in many parts of the world.

2. The most important types of malaria are those due to *P. vivax* and *P. falciparum*.

3. Quartan malaria (*P. malariae*) is much less common but has the greatest tendency to relapse.

4 The classical temperature curves of the various types of malaria are frequently not evident in the primary attack. With cerebral malaria coma may even occur without fever.

5 In endemic areas the diagnosis of malaria should be considered in any undiagnosed condition, febrile or nonfebrile. Acute surgical conditions are frequently simulated by this disease.

6 The laboratory is of the greatest aid in diagnosis. If malaria is suspected and thick smears are taken at proper intervals the clinical diagnosis can usually be confirmed.

7 Suppressive therapy frequently alters the clinical manifestations of malaria and makes the parasites difficult to find.

8 The mortality of benign tertian and quartan malaria is very low in patients treated adequately. *P. falciparum* (malignant tertian) malaria has a higher mortality rate and when pernicious manifestations (algid and cerebral types) occur it may exceed 25 per cent. With proper treatment, however, the mortality is very low.

9 The clinical features of the common types of malaria are discussed and cases presented to illustrate the varied manifestations and some of the problems in diagnosis.

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# THE LABORATORY DIAGNOSIS OF MALARIA

CAPTAIN ERIC DENHOFF

MEDICAL CORPS, ARMY OF THE UNITED STATES

IN this clinic we wish to describe the methods which have been used with success in the laboratory diagnosis of malaria in a large Army hospital operating in the South and Southwest Pacific theater of war.

The finding of malarial parasites, pigmented leukocytes and an increased percentage of monocytes is the outstanding consideration in making a laboratory diagnosis of malaria. However, a positive diagnosis should not be made unless parasites are found in the blood. In less than 40 per cent of patients with clinical malaria, who have been taking suppressive antimalarial therapy, will parasites be found in the initial blood film, and in these many of the parasites will be atypical in appearance. If blood films are examined at intervals from four to six hours, rather than correlating the examination of films with the febrile course of the disease, in many cases parasites will be found before the sixth smear is taken. However, careful preparation and staining of the blood films is necessary. We have had excellent success in finding malarial parasites because of meticulous regard for these principles.

## THE "THICK-THIN" SMEAR

**Preparation**—When a large number of blood examinations for malaria are to be performed or when the parasites are scanty, as in soldiers taking suppressive antimalarial therapy, it becomes essential to use the thick smear for diagnosis. It has been estimated that one can examine twenty-five times more blood on a thick film in one-sixth of the time necessary to examine a thin film. The thin film is used to differentiate parasites which are difficult to identify on the thick film. It is placed on the same slide as the thick film as a matter of convenience. A heavy mark is drawn with a wax crayon about three-fourths of an inch from one end of the slide which is unscratched and clean. One of the patient's fingers is cleansed, dried and pricked with a lancet. A drop of blood about the size of a small pea is placed on the smaller area of the slide. Utilizing the ball of the finger as a spreader, the drop is spread to about the size of a five-cent piece, and thin enough at the center to see the hands of a watch through the film. The thin smear is prepared by placing a small drop of blood on the opposite end of the slide and, with a second slide, spreading the blood thin enough so that the cells do not overlap each other. The slide is air-dried in a horizontal position and under a screen if flies are about.

**Staining the Thick Smear**—The thick smear may be stained when it appears to be dry. There are several technics which may be used. In our laboratory we use one of the following three methods.

1 Standard Giemsa's Staining Method—The most dependable stain is obtained with a Giemsa's staining solution. The thick portion of the smear is placed in a solution\* which will dissolve the red blood cells and fix the parasites and white blood cells. The smear is fixed for ten minutes, care being taken not to immerse the thin film in the solution. The slide is removed and washed thoroughly in neutral distilled water. Freshly filtered stock Giemsa's staining solution diluted one part with fifteen parts of a buffer solution,† or with ten parts of neutral distilled water, is placed on the thick portion of the slide and allowed to remain for twenty-five to thirty minutes. The film is then flushed thoroughly washed in distilled water and air-dried in the vertical position.

2 Rapid Wright-Giemsa Staining Method—Recently new rapid methods for staining thick smears have been devised. They are of great help when many slides must be examined or when a rapid diagnosis is desirable. A stain combining Wright's and Giemsa's stains reduces the staining time to ten minutes.‡ The stain§ is diluted one part to ten parts of neutral distilled water and poured on the thick portion of the slide. Ten minutes is allowed for staining. The stain is flushed from the film, the slide washed for one minute in neutral distilled water and air-dried.

3 Field's Method—We have had excellent results with a rapid stain described by Field.¶ The film is dipped for one second in solution A,§

\* Dehemoglobinization solution—5 cc formalin 1 cc acetic acid 94 cc. distilled water (Magnesium sulfate solution [1:1000], freshly made, will also produce excellent dehemoglobinization.)

† The buffer solution is prepared by dissolving 947 gm of dibasic sodium phosphate (Merck) and 908 gm. of monobasic potassium phosphate in distilled water making each solution up to 1000 cc. The proportion of acid and alkaline phosphates may be adjusted to any pH. Usually for blood smears a pH of 7.0 is desired. This is made by mixing 611 cc. of one fifteenth molar solution of disodium (hydrogen) phosphate ( $M/15 Na_2HPO_4$ ) and 389 cc. of one fifteenth molar solution of monobasic potassium phosphate ( $M/15 KH_2PO_4$ ). In the tropics we have more success using a pH of 6.4. This is made by mixing 713 cc. of one fifteenth molar solution of disodium (hydrogen) phosphate and 287 cc. of monobasic potassium phosphate.

‡ Rapid Wright-Giemsa stain is prepared by dissolving 2 gm of Giemsa's powder in 100 cc. of glycerin (C.P., from a freshly opened bottle). This is heated in a water bath at 55 to 60 C. (for two hours, mixing well at intervals). When this is dissolved, 100 cc. of aged Wright's stain (previously made by adding 2 gm of Wright's powder to 1000 cc of methyl alcohol) is added to the mixture and allowed to stand overnight. The amount of stain needed for a few days is filtered into a bottle.

§ Solution A of Field's stain is prepared by dissolving 13 gm of medicinal methylene blue and 5 gm of dibasic sodium phosphate (Merck) in 50 cc of distilled water. The solution is brought to a boil and evaporated to dryness (this is the most important step in preparing a good stain). Add 6.25 gm. of monobasic potassium phosphate (Merck) dissolved in 500 cc. of distilled water. Mix well and let stand for a few hours before using. Solution B is made by dissolving 5 gm. of dibasic sodium phosphate and 6.25 gm of monobasic potassium phosphate (Merck) in 500 cc. of distilled water. Add 1 gm. of eosin Y. (This solution must be replaced when it becomes greenish.)

and then dipped immediately in clean water until the stain ceases to flow from the slide. It is then dipped into solution B for one second, flushed, rinsed gently in clean water, and air-dried in the vertical position. There may be slight variations in timing with different batches of stain.

*Staining the Thin Film*—After the thick portion of the smear is stained and dried, the thin film is ready for staining.

1 *Standard Stains*—The thin portion may be stained with either Wright's or Giemsa's stain. The reader is referred to a standard textbook for these techniques.<sup>3</sup> When Giemsa's stain is used in staining the thick portion of the smear, if the thin portion is first fixed in 95 per cent methyl alcohol, the entire slide may be stained simultaneously.

2 *Combination Wright-Giemsa Stain*—We have found that a combination of Wright's and Giemsa's stains gives nearly perfect results for examining parasites and red blood cells. Frequently, because of variations of batches of stain or because the technician may overstain the film when using Wright's or Giemsa's alone, it becomes difficult to find parasites. The following technic corrects this fault. Fourteen to sixteen drops of Wright's stain are floated in the center of the thin film. This is allowed to stand for one-half to one minute to fix the stain. Then it is diluted with twenty-four to twenty-six drops of buffer solution or distilled water. The mixture is allowed to stand for eight to twelve minutes. The slide is washed well with water. The smear is then decolorized by adding a few drops of 95 per cent methyl alcohol until it is a pale pink color. Freshly filtered stock Giemsa's stain is diluted with fifteen parts of the phosphate buffer solution or distilled water and placed in a petri dish. The thin portion of the smear is now placed face down in contact with the stain in the petri dish for twenty to thirty minutes. It is then washed and dried.

*Examination*—The appearance of the malarial parasites in the thick smear is very different from that in a thin smear. In the thin smear the parasite with its typical red-staining chromatin dot and blue pigment is found fixed in the infected red blood cell. In the thick smear the red blood cells are destroyed leaving the parasites free and concentrated. Under oil immersion and using the 5x ocular, the thick smear is examined at the junction of the central heavily stained portion and the lighter periphery. This portion is clearly seen when the slide is placed on a white background. It is in this zone that the inexperienced examiner has least difficulty in finding parasites. In a smear which contains parasites, the chromatin dots stain bright red to a deep crimson and can be easily seen. These dots are associated with blue cytoplasm. The parasite is then examined with the 10x ocular for greater detail. It is difficult to identify the young forms of parasites unless the thin smear is examined. It should be prepared thin enough to compare the individual red blood cells with each other and in such a manner that there is a well-defined edge parallel to and about one-eighth of an inch

from the edge of the slide. Parasites, like polymorphonuclear leukocytes, tend to cling to the edge

*Identification of Parasites*—As the morphology of malarial parasites in thin preparations has been adequately described<sup>1 5 6</sup> only the essential differential criteria will be outlined. The early trophozoite stage of *Plasmodium vivax* is characterized by a "signet-ring" appearance consisting of a heavy red chromatin dot and a large blue cytoplasmic circle. As the trophozoite grows there is a gradual thickening of the cytoplasm and an increase in chromatin. Small yellow-brown granules of pigment appear in the cytoplasm, increasing in number with the age of the parasite. The parasite practically fills the red blood cell in thirty-six to forty hours and becomes the schizont which is characterized by masses of chromatin, and strands and particles of cytoplasm. The schizont divides into twelve to twenty-four merozoites, each consisting of a dot of chromatin and a small portion of cytoplasm. The macrogametocyte has a dark blue cytoplasm, a small dark red chromatin mass and abundant dark brown pigment scattered through the cytoplasm. The microgametocyte has a light cytoplasm and a larger, more diffuse chromatin. When full grown the gametocyte is the size of a red blood cell. With infections due to *Plasmodium vivax*, the infected red blood cell is paler and larger than normal.

*Plasmodium falciparum* usually appears in the blood stream either as the young trophozoites or gametocyte. Only in very severe cases of subtertian malaria will older trophozoites or schizonts be found in the blood. The parasite is characterized by a small threadlike cytoplasmic circle and one or two small chromatin dots. The gametocyte is sausage-shaped, about one and one-half times as large as a red blood cell with a compact chromatin mass in the center associated with golden pigment and a blue cytoplasm in the periphery.

*Plasmodium malariae* resembles *P. vivax* with the following exceptions: the infected red blood cell is normal or slightly smaller in size, the "signet-ring" form is smaller, thicker and heavier, and as the parasite grows the pigment becomes more abundant and coarser with a tendency to form around the periphery of the cytoplasm. The merozoites number six to twelve. Gametocytes resemble *P. vivax* but are smaller and more heavily pigmented.

In the thick film, young parasites of all species appear alike. They do not necessarily appear as complete rings but may appear as chromatin dots associated only with a portion of a cytoplasmic circle. These forms are described as "exclamation marks," "commas," or "interrupted rings." The older trophozoites of *P. vivax* exhibit a tendency for the cytoplasm to be fragmented and arranged in clusters. The cytoplasm stains blue and the chromatin a bright red to deep crimson. The pigment is scattered on the background of the film. Those of *P. malariae* exhibit a heavy dark pigment in compact cytoplasm. The chromatin is not conspicuous and the pigment tends to be heavy, dark

brown, and arranged in bands. As growth progresses, the cytoplasm of *P. vivax* and *P. malariae* becomes less tenuous and more compact. The adult schizont resembles the parasite in the thin film. In the thick film it is frequently impossible to distinguish macrogametes of either *P. vivax* or *P. malariae* from the adult trophozoite. The microgametocyte is more easily determined because of its large, rounded nucleus surrounded by light-staining cytoplasm containing numerous grains of heavy pigment. The nucleus stains more deeply than in the thin film. The gametocyte of *P. falciparum* resembles that in the thin smear.

Early ring forms of *P. vivax* are difficult to distinguish from the trophozoites of *P. falciparum*. This is especially true in mixed infections. The differentiation in diagnosis is assisted by the fact that the young trophozoites of *P. vivax* are nearly always associated with older forms of the parasite, while *P. falciparum* are more consistent in size and shape. A smear repeated in twelve hours may clarify the diagnosis by presenting definite schizonts of *P. vivax*. As a rule, a thin smear is necessary to determine the type of plasmodium.

**Sources of Error**—The microscopist may be confused in the examination of thick films by contaminants from poorly cleansed fingers or slides, or by yeasts, molds and fungi frequently found in distilled water. If unscratched slides are used, if slides are properly cleansed with soap powder and water, dipped into ethyl alcohol, and dried with a fine nonlint cloth, and if the water from the staining dishes is changed frequently, the incidence of artifacts will be minimal. Slides should never be blotted dry, as this will destroy the morphologic characteristics of the parasite. Platelets are loose and spongy, while "basket cells" are characterized by a loose mesh network without chromatin material. When Field's stain is used, the examiner will find many eosinophilic staining granules scattered through the smear. Although some of these may be chromatin material, they should not be called parasites unless they are associated with blue cytoplasm.

#### CONCLUSION AND SUMMARY

The laboratory diagnosis of malaria is not difficult if meticulous regard is paid to certain cardinal principles: (1) The blood should be examined at intervals of four to six hours rather than before or during a febrile attack. (2) Proper fixation and staining of the blood film is the basis for facilitating the finding of parasites. (3) A basic knowledge of the appearance of the parasites in the thick and thin film is necessary before a diagnosis can be attempted. (4) Parasites are atypical in appearance, fragmented, or degenerate in soldiers taking suppressive antimalarial drugs.

The rapid method for staining thick films is ideal in situations in which a large number of films must be examined daily or when the diagnosis must be made as rapidly as possible. In order to treat malaria

patients properly, it is essential that the clinical impression be confirmed by finding malarial parasites in the blood

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## SCRUB OR MITE TYPHUS\*

(Tsutsugamushi Disease, Bush Typhus, Japanese River Fever, Sumatra Mite Fever, Rural Tropical Typhus, etc)

COLONEL GARFIELD G DUNCAN

MEDICAL CORPS, ARMY OF THE UNITED STATES

SCRUB or mite typhus is caused by the *Rickettsia tsutsugamushi* which is conveyed to man from infected lower animals, notably rodents, by the larva of the mite, *Trombicula akamushi*. This is in contrast to the other rickettsial diseases, namely Rocky Mountain spotted fever which is transmitted by the tick, European or epidemic typhus by the louse and murine typhus by the flea.

The mites inhabit the banks of streams, the edges of woods, areas covered with kunai grass, decaying logs and stumps and are most prevalent during the wet season. The reservoir of scrub typhus infection is frequently localized to small areas. A distance of one hundred yards or less may mark the distance between dangerous and safe zones.

Scrub typhus is endemic in considerable portions of the Southwest Pacific War Zone and it is probable that as the Allied forces proceed northward this malady will be encountered in widely separated areas. Scrub typhus has not been a problem of much military importance to the Allied armies to date, its mortality having been low in contrast to the Japanese prewar figures of 20 to 60 per cent. Success will reward appropriate treatment in most cases provided it is begun in the early stages of the disease. An early diagnosis is vital if the full advantage of complete rest, so important in the management of these patients, is to be gained. Medical officers in the Pacific theaters of war must be on the alert for evidences of this disease if needless tragedies are to be avoided.

### CASE REPORTS

CASE I—A white soldier, aged twenty-five years, was admitted to a military hospital on November 22, 1943, complaining of fever, headache and general body aches. On the previous day he had noticed a small painless lesion 2 inches above the left nipple which he believed to have been caused by an insect bite. He claimed to have been in good health until the day of admission.

*Physical Examination*—The positive findings were: Patient well nourished but acutely ill, exhibiting evidences of a marked toxemia, body temperature 100.8° F, pulse rate 84, respirations 22 per minute, blood pressure 105 mm systolic.

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\* The author is grateful to Lt Colonel Bruce P Webster for access to information which he collected on this subject, and to Lt Colonel H I Sigmund and to Major A H Zieman for their cooperation as Chiefs of the Medical Services on which most of these patients were observed.

and 70 mm. diastolic, mild hyperemia of the nasal mucous membranes and of the pharynx, mild conjunctivitis, slight enlargement of all peripheral lymph glands, a small "eschar" with a surrounding area of erythema 2 inches above the left nipple, and tenderness in left upper quadrant of the abdomen. There was no demonstrable skin rash.

*Progress Notes*—There was little change in the patient's condition until November 28 when the intensity of the headache became severe and difficulty in breathing was noted. Also, there was tenderness over the left posterior auricular and left axillary lymph glands. The patient's condition became progressively worse with intractable headache and increasing evidence of toxemia until, on December 1, he was critically ill. He complained of tightness of the chest. A troublesome cough developed and crepitant rales were heard at the base of each lung. The respiratory rate was increased to 44, the pulse rate to 130 per minute and the fever was continuous, remittent in type. The spleen had become palpable and tender. On December 2 there was increased listlessness and there was looseness of the bowels. On December 3 definite signs of pneumonia were elicited at the base of each lung, the disease being more advanced on the right side. Restlessness became marked, the pulse volume was reduced with a pulse rate of 140 per minute, and cyanosis became noticeable.

On December 4 the patient was semistuporous, voided involuntarily, had muscle tremors with jerky movements of the limbs, and abdominal distention was present. Irregular rapid, shallow respirations, cyanosis and profound toxemia preceded his death on December 5.

*Laboratory Data*—Examination of the urine revealed no abnormalities on November 23 and 25. A trace of albumin appeared in the urine on November 29 and a moderate amount was found on December 2.

The blood counts were as follows:

	Leuko- cytes	Segmented Forms (per cent)	Stab Forms (per cent)	Eosin- ophils (per cent)	Lympho- cytes (per cent)	Mono- cytes (per cent)
Nov. 23	6,500	60	15		25	
Nov. 29	8,400	56	14	1	27	2
Dec. 1	14,000	56	24		20	

Red blood cells, 4,800,000. Hemoglobin, 90 per cent.

On December 3 the serum agglutination of the OAK strain of *B. proteus* was positive in dilutions of 1:320. Blood smears were found to be negative for malarial parasites.

*Diagnoses*—1. Typhus, scrub endemic. 2. Pneumonia, lobular.

*Treatment*—The management of this patient consisted of complete rest in bed, liquid and soft diet, dextrose and normal saline solutions intravenously, plasma and oxygen therapies, sulfadiazine and the liberal use of morphine.

*Case II.*—A white soldier aged twenty years, was admitted to the hospital on December 5, 1943, complaining of chills and fever of five days duration. Also pains in the eyes, severe headache and nasal obstruction had developed on the day of admission.



*Physical Examination*—The patient appeared quite ill. He had a marked conjunctivitis and injection of the nasal mucous membranes, a maculopapular rash which was prominent on the thorax and feet. There was a papule with a black center (eschar) in the right para-umbilical area. Both the liver and spleen were slightly palpable and tender and the peripheral lymph glands, particularly the right inguinal glands, were markedly enlarged and tender.

*Progress*—Insomnia, headache, nonproductive cough and restlessness were especially troublesome. The fever was remittent in type. On December 9 crepitant rales were heard over the base of each lung and there were many premature cardiac systoles. The skin rash had disappeared. The patient was afebrile after December 11 and convalescence was uncomplicated.

*Laboratory Data*—The red blood cells numbered 4,900,000, hemoglobin was 90 per cent, the leukocyte count 5400, polymorphonuclear forms 56 per cent and lymphocytes 44 per cent. The urine was normal on entrance but contained a moderate amount of albumin on December 11. On December 20 and 27 the blood serum agglutinated OXK strains of *B. proteus* in dilutions of 1:320, and on December 31 in dilutions of 1:40. The serum failed to agglutinate the OX 19 strains.

*Diagnosis*—Scrub typhus.

*Treatment*—The therapy consisted of complete rest in bed, liquid and soft diet, sedation, and the administration of polyvitamins. Penicillin, 40,000 Oxford units, was given intravenously but it is unlikely that it had any beneficial effect.

### COMMENT

The two cases selected for presentation represent the two extremes—the mild form proceeding to uncomplicated convalescence and a form sufficiently severe to cause death. In the general discussion that follows it will be observed how closely these two cases parallel the typical clinical manifestations of this disease.

*Onset*—In neither case was the *incubation period* known though it ordinarily varies from seven to eighteen days but most frequently it is between seven and ten days.

Each patient had an *initial cutaneous lesion* containing a crust or “eschar” appearing presumably as the result of the bite of the mite larva. This initial lesion is frequently absent. *Swelling and tenderness of the lymph glands*, through which the lymph from the “eschar area” is drained, is observed in nearly all cases.

*Symptoms*—*Intractable headache* is common to nearly all of these patients. Indeed, without this symptom one must observe caution in making the diagnosis of scrub typhus. *Fever, general body aches, severe backache and pains in the eyes* are outstanding complaints and *vomiting, hiccoughs and epistaxis* are frequently encountered. *Cough* is likely to be troublesome in the second week of the acute stage of the disease and the *respirations become rapid and shallow*. A transitory *deafness* occurs in over one third of the patients in some outbreaks and is rare in others. *Diarrhea* is a frequent complaint as is *insomnia*. Several patients complained of localized areas of *numbness* during convalescence.

**Physical Findings.**—These patients may be only slightly ill on admission. Indeed, they may object to being hospitalized for what they consider a trifling illness. As the disease progresses the course may be mild or grave. A widespread distinctive reddish *maculopapular rash*, which blanches on pressure in the early stages, appears in abundance over the body and face with milder involvement of the extremities as early as the fourth day of the illness. The spots vary from 2 mm to 0.5 cm in diameter. The rash may subside early but more often the process increases in intensity until about the tenth day when it begins to fade, leaving faint gray to brownish pigmented mottling in the involved areas which may be observed well into the convalescent period. Over one half of these patients exhibit the initial lesion, the "eschar." In some outbreaks nearly 100 per cent show this abnormality.

Among the common findings are a *conjunctivitis*, *subconjunctival* and *retinal hemorrhages*, *nystagmus*, *muscle tremors* and *weakness*, a *softening of the heart sounds* and occasionally a *slight enlargement of the area of precordial dullness*. Signs of an *atypical pneumonia* are common, with moderate *cyanosis*. *Abnormal electrocardiographic tracings* may be observed during the acute phase but these subside early in convalescence.

The *pulse rate*, as a rule, is not increased in proportion to the fever though *tachycardia* may appear in the second or third week, when it is an unfavorable sign. A *dirotic pulse* is remarkably frequent. The fever is continuous, oscillating for the most part between 100 and 104. The fever tends to increase gradually reaching the highest levels between the tenth and the fourteenth days. It then subsides by lysis though the severity of the clinical signs of the disease is abruptly reduced before the temperature is restored to normal. There is *enlargement of all peripheral glands* but especially those in the region of the "eschar." Some outbreaks of the disease manifest a high incidence of *extensive involvement of the meninges*. This, with basal brain involvement—*meningo encephalitis*—causes stiffness of the neck muscles, *nystagmus*, unpredictable pupillary changes, headaches of exquisite severity, increased tendon reflexes, positive Kernig's sign and increased intraspinal pressure. A *hepatitis with jaundice* occurs occasionally. The *spleen* is frequently palpable and tender. A marked *loss of weight* is invariable. The "typhoid state" with muttering delirium is not uncommon. Signs of a *collapse of the peripheral circulatory system*—pallor, respiratory distress, pulse weak and thready or unobtainable, with a pronounced fall in the blood pressure—giving the indications of imminent death may appear with remarkable abruptness. The importance of the early recognition and treatment of this dangerous complication cannot be overemphasized.

**Laboratory Data.**—A "febrile albuminuria" occurs as the disease reaches its greatest intensity. The *blood count* is normal or leukopenic with a moderate to a marked lymphocytosis. A leukocytosis occurring

late in the acute phase of the disease should suggest the presence of a complication and is considered an unfavorable sign. The *spinal fluid* is clear but, in patients having a meningo-encephalitis, is under increased pressure, and shows a moderate increase in the number of lymphocytes and a reduction in the chloride content. The *blood serum agglutinates the OXK strain of B proteus* in increasing titer after the tenth day. Agglutination occurring in dilutions above 1:160 is considered to be significant. This property rapidly subsides after the third week of the disease. There is little or no agglutination of *B proteus* OX 19. In some instances there is a reduction of the *plasma albumin* below normal values. Rickettsiae bodies may be observed in blood smears.

**Prognosis**—A marked lymphocytosis, a low fever and generalized enlargement of the lymph glands are considered to be *favorable signs*. There is some evidence that outbreaks of this disease with a high incidence of "eschars" carries a lower mortality than those in which this lesion is infrequent. It is possible that this lesion appearing early in the disease initiates an immune mechanism which may ameliorate the acute manifestations which follow.

A high fever, an increasing pulse rate, the absence of lymphocytosis with a leukocytosis with signs of a meningo-encephalitis are *unfavorable omens*. Overweight influences the prognosis unfavorably and patients over forty years of age do not do as well as those who are younger. In the fatal cases death usually occurs in the latter part of the second or in the third week. Death may follow collapse of the peripheral circulation, acute myocardial failure, or, as occurs frequently in some outbreaks of this disease, an extensive meningo-encephalitis.

**Pathological Changes**—The outstanding abnormalities are necrosis, intimal swelling with some tendency to thrombosis involving the small blood vessels in all organs of the body. These changes are particularly intense in the brain substance, meninges, skin and the myocardium with diffuse and intense widespread perivascular round cell infiltration. Examination of the lungs usually reveals a lobular pneumonia.

The initial lesion or "eschar" varies from a minute spot to 0.5 cm in diameter. It is black and firm with a necrotic base or crater and a surrounding area of erythema. The initial lesions may appear on any part of the body. The writer has observed them on an eyelid, on the neck, in the axillae, on the trunk, about the genitalia (scrotum, perineum and prepuce) and infrequently on the legs and feet. The "eschar" falls off shortly after the onset of the acute phase of the disease, leaving a shallow ulcer which is rapidly repaired.

**Prevention**—Localities known to harbor foci of the disease, and poorly drained kunai grass areas should be avoided when possible. It is important to avoid sitting or lying on the ground, especially in kunai grass or on decaying logs and to keep to paths, which are sanded

or graveled, and to roads when this is possible. Abandonment of locations found to be infested with mites and infected rodents may be practicable. Areas may be made safe by clearing all kunai grass in the camp site and immediate vicinities. If the grass cannot be burned as it stands it is cut at the level of the ground, collected and burned. Shrubbery and decaying vegetation are removed or burned. Native labor may be available for this task. The native laborers apparently have an immunity, acquired or natural, to scrub typhus. Spraying with insecticide or oil of areas upon which tents are pitched is advocated.

The eradication of rodents will reduce the reservoir of infection and should be executed with unrelenting vigor.

Impregnation of clothing with dimethyl phthallate insect repellent will reduce the likelihood of infection when it is impossible to avoid areas known to harbor the mites or areas providing a favorable habitat for these insects. The repellent should be thoroughly smeared over shoes, socks, leggings, trouser legs, trouser fly, waist of trousers, open edge of shirt in front and about the neck. This application will protect for several days and will withstand washing in cold water. The repellent is also applied directly to the extremities. Insecticide powder is applied about the waist and ankles and inside the leggings and jungle boots.

On returning from infested areas it is desirable to go over the trunk and extremities (avoiding genitalia) lightly with a cloth moistened with kerosene to bathe well and put on fresh clothing.

The immediate prospects of securing an immunizing vaccine to protect against this disease are not unfavorable.

*Treatment—Complete Rest in Bed in Fowler's Position During the Acute Phase*—Under no circumstances should these patients be subjected to needless transportation. The patient is not allowed to sit up or to feed himself. He is assisted in turning in bed and is lifted on the bed pan. Special nursing care is essential.

*Diet*—An adequate diet is of utmost importance. Liquids are given during the acute stages returning gradually to soft and to a full diet as convalescence is established. (Suggestions: Cereal diluted with milk, crushed bananas, milk toast, cream soups [add butter], crushed crackers with milk and sugar, eggnogs, canned pears, peaches, juices of other fruits, hot toast with liberal helpings of butter, milk, etc., and any food desired by the patient, if available. Small frequent feedings are desirable. Nourishments at 0600, 0900, 1200, 1500, 1700, 2000 and 2400 hours are recommended.) The administration of fluids through a small tube passed through a nasal passage to the stomach may be practicable in some cases. The diet is fortified with polyvitamins.

*Liquids*—A minimum intake of 3500 cc in each twenty-four hours during the febrile stage is desirable. An output of urine in excess of 1000 cc in twenty-four hours is a good indication of a satisfactory fluid balance.

*Drugs*—1 Morphine to control insomnia, restlessness, intractable headaches, vomiting and hiccoughs is indicated in doses of 0.016 gm ( $\frac{1}{4}$  grain) Sedation is invaluable

2 Cardiac stimulants are contraindicated

3 Digitalis is *not* indicated except in the event of cardiac decompensation or auricular fibrillation

4 Mineral oil, 15 cc ( $\frac{1}{2}$  oz), is given each evening Dehydrating laxatives are contraindicated An enema is given every third day if necessary

*Emergency Measures*—1 Blood plasma, glucose and saline solutions parenterally may be indicated during acute episodes when food and liquids are not retained All fluids given by vein should be introduced very slowly, not to exceed 5 cc per minute Intravenous therapy should be kept at a minimum in view of the acute damage to the myocardium

2 Oxygen therapy is indicated in the presence of cyanosis and pronounced respiratory distress It is preferable to administer the oxygen for prolonged periods rather than for a few minutes at one time

3 Lumbar Puncture—The slow and moderate reduction of the elevated intraspinal pressure is especially valuable in relieving headaches, vomiting and hiccoughs

4 Epinephrine (adrenalin) 1:1000 in doses of 0.5 cc is of inestimable value in event of collapse of the peripheral vascular system The initial dose is given intravenously It may be advisable to follow this measure with the slow parenteral introduction of 500 or 1000 cc of blood plasma or 500 cc of a glucose solution, 10 per cent, to which 0.5 cc of epinephrine has been added

5 Blood Transfusions—Benefit from either transfusions of whole blood or immune serum is not established

*Hospitalization*—Patients having scrub typhus should be retained in the hospital for four to six weeks after all evidences of the acute phase have subsided

## THE DENGUE FEVERS

MAJOR DAVID Q. EWING

MEDICAL CORPS, ARMY OF THE UNITED STATES

To the medical personnel of a large hospital serving in the South and Southwest Pacific theaters of war, dengue and related fevers were diseases which we all remembered vaguely from lectures on tropical medicine in medical school, and from a brief refresher course in tropical diseases, self-administered, as we spent lazy days aboard an Army transport crossing the great breadth of the Pacific Ocean. Few of us had ever seen a patient suffering from dengue, and only one of the officers had ever had the disease.

The first two cases of dengue which we encountered were not recognized despite the fact that they displayed classical signs and symptoms. The first appearance of dengue occurred among the nurses of the hospital. One young woman was admitted to the hospital after being rescued from a submerged sedan which had been swept off a flooded bridge near the hospital. A few hours after admission she became acutely ill, with high fever, slight sore throat, chilliness, and severe aches and pains in the back and limbs. She complained bitterly that any movement of the eyes caused her the greatest discomfort. Examination of the patient revealed no abnormality except a slightly inflamed soft palate and moderate injection of the conjunctivae. On the third day, the patient's temperature was normal and she announced that she felt well enough to leave the hospital. However, her temperature rose suddenly to 103° F. and the pains in the back and extremities returned and there was an almost intolerable pain "behind" her eyes. On physical examination only a dull red blush of the palms of the hands and soles of the feet was noted. She was extremely prostrated. The following day her fever began to fall and in another day the temperature was normal. Except for weakness and mental depression, she felt well. She remained in the nurses' ward for two additional days and was then discharged to quarters. Two days later she reported on sick call, complaining that she could not sleep at night because of marked itching of the soles of the feet and palms. On examination the only abnormal finding was a slight desquamation of the skin of palms and feet.

In view of this unusual finding we considered the possibility of her having had some unusual illness. The temperature chart revealed an initial high fever, with a fall to normal on the third day, a secondary rise to a point higher than her first elevation, and a return to normal on the sixth day. The blood count, which at first glance had been normal, showed a moderate leukopenia, with a relative lymphocytosis.

Urinalysis was negative. Questioning her, we learned that one week prior to the onset of symptoms she had visited a coastal town, several hours' travel away, in which dengue fever was epidemic. Not many of the inhabitants of the town were affected, but troops stationed nearby were being hospitalized.

This was our introduction to dengue fever—and this patient, and others who followed her, impressed the characteristics of the disease indelibly on our minds.

The disease, while endemic in tropical and subtropical areas, may strike with great suddenness in epidemic form, extending even into the coastal areas of countries in the temperate zone, where it may incapacitate large portions of the population of towns and cities for short periods. The threat of dengue and related fevers to the armed forces engaged in war in the tropics can scarcely be overemphasized, especially in view of the effectiveness of preventive measures in keeping troops well and in fighting trim. It is a singular circumstance that dengue is so little known medically. This is due to the fact that few medical officers have ever seen a patient suffering from dengue, and to the lack of information on the disease, except for sporadic articles in medical journals and in government reports. Examination of reports on dengue fever from all over the world reveal striking similarities and equally glaring differences. There is frequent conflict of undoubtedly good clinical descriptions, for instance, which gives rise to the important consideration of whether or not dengue fever is a distinct clinical entity. The probability is that the term "dengue fever" covers a group of diseases, caused by different strains or types of a filtrable virus. For that reason, this article has been headed, after due consideration, "The Dengue Fevers."

#### HISTORY

The early history of the disease is scant and obscure, a fact that is all the more striking because the disease is capable of striking down almost the entire population of cities. Recent investigations have tended to substantiate the accuracy of detail in an epidemic in Guadeloupe as early as 1635, where it was called *coup de barre* or "the blow of a club." Even at that early date there was a tendency to confuse dengue with yellow fever, which has an identical vector, *Aedes aegypti*.

Three accounts of outbreaks of dengue appeared almost simultaneously in 1779 and 1880, in three spots almost equally spaced around the globe—Cairo, Batavia and Philadelphia. The now famous report of the disease in Philadelphia by Benjamin Rush is still a classic, and is of even more interest because he wrote of dengue as compared with yellow fever, both of which he saw frequently, side by side. It is to Rush that we owe perpetuation of the term "breakbone fever," which term, he says, was "its more general name among all classes of people."

Rush's powers of observation did not omit the presence of severe mental depression which is often a feature of the disease as we have encountered it

In the South Pacific in the present war, one of the outstanding qualities of dengue fever has been its dramatic suddenness of onset. The stricken patient is often able to name the moment of onset, almost to the minute. This is strikingly illustrated in an account as far back as 1779, which was written by David Bylon (who was "Stads Chirurgyn" to the city of Batavia) and reported by O H Perry Pepper in 1941. Bylon, who himself contracted dengue, reported that he was well until 5 P.M. when, he continues, "I noticed a gnawing pain in my right hand, and in the joints of the hand and arm which gradually increased, extending to the shoulder and then over my entire body, so that at 9 o'clock that evening I was in bed with a high fever. I had a restless and sleepless night, suffering severe pains over the entire body, especially in the legs and arms and in the joints. Soon my face began to swell, with a light rose-colored rash which covered the whole surface of the skin and was accompanied by considerable swelling. This is a brief notice concerning a very well-known disease which, however, in the memory of man here in Batavia has never reached an epidemic, and which has, therefore, seemed wondrous to the inhabitants." This account almost certainly described true dengue fever, which has long been known in Java and where neither sandfly fever nor yellow fever was present to cause confusion in diagnosis.

#### DEFINITION

Dengue is an acute exanthematous, noncontagious fever caused by a specific filtrable virus of probably differing immunological types, of wide tropical and subtropical distribution in numerous foci, and occurring in epidemic and pandemic forms biologically transmitted by at least two vectors, *Aedes aegypti* and *Aedes albopictus*. The immunity conferred by one attack is highly variable. The disease runs a benign course, characterized by sudden onset, with fever, postorbital pain, headache and pains in the extremities, alterations of taste, rashes and a normal or lowered leukocyte count. The initial rise of fever lasts three to four days followed usually by a brief one or two-day remission, a second rise then succeeding and lasting in diminishing scale for two to three days. It is almost never fatal, it occurs in subclinical and in almost inapparent forms, and naturally affects all mankind and monkeys of some species.

#### GEOGRAPHICAL DISTRIBUTION

Dengue and related fevers occur mostly in tropical and subtropical countries, their distribution almost exactly conforming to the range of their vector, the *Aedes* mosquito, abounds. It may occur in certain temperate zones during the warm months, the arrival



from the tropics being blamed in several instances. In the United States, dengue has usually been limited to the states bordering the Gulf of Mexico, but cities farther north including Boston, New York and Philadelphia have been affected sporadically. The long-pondered question as to the cause of sudden epidemics in ordinarily endemic regions (those that are warm enough the year round to allow the vectors to breed) may be answered some day in the discovery of a lower animal reservoir for the infection. The influx of susceptible individuals into an endemic area has often been the signal for an outbreak of dengue, while the incidence among the native population remains at a low level in the same locality. We observed this phenomenon in a coastal town some distance from our hospital site, where soldiers were stricken but natives of the town escaped almost entirely.

In general, the distribution of dengue fever throughout the world can be delineated by naming its northern and southernmost extensions. These are, with a few exceptions, latitude  $36^{\circ}$  North, to latitude  $35^{\circ}$  South of the equator. In the United States this line runs west from Raleigh, through Nashville, Santa Fe, to a point halfway between Los Angeles and San Francisco. Continuing westward, the northern limit is in southern Japan, eastern China, southern Russia, particularly around the Black and Caspian Seas, Turkey, Greece, Sicily, southern Spain and the Azores.

The southernmost limits of dengue may be roughly marked by a line beginning at Buenos Aires and extending westward to the southeastern coast of Australia and then along the coastal belt of Australia from Queensland to Port Darwin to Carnarvon in Western Australia. In Africa, endemic areas of dengue extend to the southernmost limits of the continent at Capetown.

#### ETIOLOGY

Ashburn and Craig, in 1907, proved that the diseases could be transmitted by injections of blood either filtered or unfiltered. In 1906, Bancroft proved that the disease is transmitted by the mosquito *Aedes aegypti*. This was confirmed in 1916 by Cleveland and his associates. A filtrable virus is known to be present in the peripheral blood of patients suffering from the disease from the day before the initial fever until the third or fourth day of the disease. Susceptible humans, but not animals, birds or reptiles, will contract the disease when the filtrate is injected subcutaneously or intravenously. There is an exception to the exclusion of all animals in that certain species of monkeys in dengue-free mountains are susceptible.

#### EPIDEMIOLOGY

The tendency toward epidemic recurrences of dengue fever, explosive and violent in their spread and ability to incapacitate great proportions of a population, is only approached by influenza. Even the

latter disease does not affect such large proportions in any one area. The probable existence of differing immunological strains of the dengue virus is thought to favor such outbreaks, especially when they occur in endemic areas. The sudden increase in the normal numbers of the vector, *Aedes aegypti*, and its shift to areas beyond its normal distribution is also a factor. The circumstances surrounding the great increase of vectors over wide geographic areas are not fully understood, but the influence of warm climate, plus plentiful or excessive rainfall plays an important part. Indeed, it may even enable the meteorologist to forecast the rapid multiplication of the vector and its influence on the morbidity rates.

Epidemics of dengue fever may occur in periods of scant rainfall and even of drought. The epidemic in Philadelphia in 1870 occurred at a time of almost total drought, and numerous other instances of this apparent paradox have been recorded. The explanation is readily found in that the necessity of utilizing cans, buckets, barrels and tanks for water storage in periods of scant rainfall thereby supplies the *Aedes aegypti* with the very means of reproduction which it prefers. A fall in temperature in any area below that usually found in the summer season almost invariably stops the appearance or persistence of dengue fever, although the occurrence of a "warm spell" in the middle of a winter season may see a short-lived outbreak.

The spread of armies over the world and the tendency of the *Aedes aegypti* to follow the lines of communication constitute an ever-present threat of infection. It is known to be carried on trains, aboard ships and transports, and on airplanes. Taylor, of the School of Public Health and Tropical Medicine in Sydney (1942), says "*Aedes aegypti* is a born traveler. I have never traveled on a long distance train in both northern New South Wales or in Queensland without finding adults of this species. In the middle of the last century, it was transported by the teamsters in their water barrels, later by motor car owners in their water bags, and now by the aeroplane."

**Reservoirs of Infection**—The insect itself is the main reservoir of infection. Once infected, it remains so for the rest of its life. Man acts as a reservoir in that his blood may infect the vector for approximately one day of the prodromal stage of dengue and for the first three to five days after the actual onset.

The question of animal reservoirs of infection is one that still remains unanswered. It is known that certain species of monkeys are a source of the virus, even while giving no outward evidence of the disease. Investigation into the possibility of other animal reservoirs, as well as the possibility that certain reptiles and birds can transmit the virus, is an important field of further investigation.

The feeding and other habits of the *Aedes aegypti* are important in that it is almost purely domestic, preferring the habitations of for breeding and living, rather than fields, forests and ponds.

observers agree that biting usually occurs in daylight, but may occur at night in the presence of a light

The insects show an average length of life, under natural conditions, of approximately six weeks. The normal range of flight is generally considered not to exceed 200 yards but some investigators, using marked insects, have recaptured specimens at 1000 yards from the point of release (Edwards, F W, 1941, quoted by Frank H Taylor, Sydney, 1942)

### IMMUNITY

Until such time as a simple and specific laboratory test for the presence of dengue is found, it appears unlikely that any great amount of progress can be made in clarifying the problem of immunity. From numerous reports of epidemics in various parts of the world, it seems certain that natural immunity is not demonstrated in any marked degree in any particular race or age group. Apparent racial immunity seems, on more careful analysis, to be more accurately explained on the basis of acquired immunity due to previous and usually repeated attacks.

It is generally recognized that the immunity conferred by an attack of dengue is extremely variable in duration. It appears to last for a period of a few months to a few years. Recurrence of the disease within a few weeks to a few months may be the result of infection by a different strain of the virus.

### SYMPTOMATOLOGY AND CLINICAL COURSE

After an incubation period of from four to ten days, the patient experiences a sudden onset of *chilliness*, *dizziness* and *fever*, with marked prostration and *headache*. *Severe aching of the legs, back and arms* is usually present. Shortly after the onset, in most patients *post-orbital pain* is noted which is accentuated by any movement of the eyes. It is doubtless this discomfort on ocular movements that gives rise, partially at least, to the frequently observed apathy of the patient.

The fever in dengue, in the large proportion of cases, demonstrates what has become known as the "saddle-back" temperature curve (see Fig 97). There are many instances recorded in which this drop in fever on the third or fourth day does not occur, but is replaced by a single elevation. Nearly all of the cases of dengue fever which we have observed displayed the saddle-back type of temperature chart.

The description of the course of dengue fever may conveniently be divided into its characteristic three phases, the primary fever, the remission and the terminal elevation.

**The Period of the Primary Fever**—The primary fever is initiated by a sudden rise to 102° or 103° F, often within an hour or two after onset. At this time the marked *erythematous blush* of the face is seen, often associated with an urticaria-like *puffiness of the skin*, most marked under the eyes. In our cases we seldom observed injection of the con-

junctions as is often reported. A moderate *redness of the soft palate and anterior faucial pillars* was noted in nearly all cases. The tongue was often coated but not inflamed. Coryza was not seen. The spleen and liver were not enlarged but in about one half of our patients there was enlargement of the cervical lymph nodes, and less frequently of the inguinal nodes. There was no tendency toward unilateral enlargement of nodes, as is sometimes reported.

The *severe aching pains* in extremities and back were bitterly complained of in the phase of the primary fever, as was also hypersensitivity of the skin. In soldiers there is often a refusal to be shaved because of "soreness" of the skin of the face.

The *appetite* usually disappears, and the forcing of fluids and fruit juices to combat fluid loss from vomiting, diarrhea or sweating often becomes a major problem. *Nausea* is present in almost all cases and vomiting in at least a third. Cases exhibiting constipation and those having loose movements were about equally divided in our series.

Many observers have reported swelling and soreness of the joints, enough at times to offer confusion with rheumatic fever. We did not observe swelling of the joints. The patients sometimes complained that knees or wrists were very painful, but on close observation the complaint centered more around muscle groups and tendon insertions than in the joints themselves.

Emphasis is often placed on the occurrence of a slow pulse during the temperature elevations but in the great majority of our cases the pulse rose in proportion to the fever, thereby removing what is often claimed as a contributing factor to diagnosis.

On the third or fourth day after onset the temperature falls to normal, or nearly so. The fall may be short-lived, the temperature rising sometimes after so short an interval that routine recordings may fail to detect the change.

**The Period of Remission**—In this phase the patient often feels so much better that he considers himself able to go about his usual duties. The pains almost entirely disappear, and except for a feeling of weakness and a tendency to perspire easily there is little evidence that the patient was ill a short time before. Contributing to the patient's impression that he is well, is the fact that the remission may last a day or two. In our cases, however, the majority showed a temperature that approached, or actually reached, normal for only a few hours.

**The Terminal Elevation of Temperature**—In most of our cases the second rise of temperature usually reached a point higher than the primary fever. Other observers report that this is not a constant feature. During this final phase, the diagnostic *terminal rash* appears. It follows the second rise of fever within a few hours, as a rule, but it may be delayed until the sixth or seventh day. Coincident with the terminal rise the aching of head, back and limbs recurs, and a state of depression usually follows.

In our experience the terminal rash was variable in extent, duration and appearance. About half the cases observed first developed a rash over the anterior thorax a few hours after the second rise of fever. The remainder first showed the rash on the extremities. The dorsal surfaces of the feet and hands were frequently affected, as well as the elbows, knees and heels. Pressure against the bed linen seemed to be an influencing factor. From these points the rash extended over the entire body in about one quarter of the cases. In a few the rash was slight and in evidence only a day or less. A nearly constant finding was a rosy blush of the skin of the palms and soles of the feet, quite characteristic in its appearance. The rash itself has been variously described, most often as resembling the rash of measles or as a scarlatiniform rash with small punctate papules, surrounded by erythematous zones, the latter tending to become confluent later.

In our cases the rash most often appeared as a diffuse erythema, starting on the anterior thorax, and spreading to the rest of the body within a few hours, sometimes resembling measles, but often displaying an urticarial element. Itching at this stage, if present, was only of moderate degree. There were no hemorrhagic phenomena, bleb formation, or vesicles.

**Convalescence**—Recovery from dengue is not to be regarded as reason for immediate resumption of usual activities. The patient finds at once that he is afflicted with mental depression and physical weakness out of all proportion to the length or severity of the illness. We found it necessary to allow a week or ten days of rest to intervene before returning those who had recovered from dengue to duty.

In at least three quarters of our cases there was intense intractable *itching* of the palms and soles of the feet, sufficient at times to prevent sleep. *Desquamation* of the skin was seldom seen, except in those patients who had resorted to rather vigorous scratching. In these a fine branny desquamation was noted but not more than might have been traumatic in origin.

#### CASE REPORTS

**CASE I**—An unmarried female nurse, aged thirty years, was admitted to the hospital on April 26, 1943, complaining of severe aching pains in legs, lower back and arms, intense headache and pain behind both eyes. Fever and great sensitivity of the skin to contact with her army uniform of shirt and trousers was present. She had been perfectly well until 4 P. M. the day before. She was particularly certain of the time of onset because she experienced great difficulty in getting to her quarters, having just come off duty. She became weak, dizzy and chilly, and found her legs almost too weak to carry her. She spent a restless night, with intense aching in her left shoulder and feverishness. The pain in the shoulder soon spread to both elbows and hands, and seemed to appear almost simultaneously in her legs and back, growing very severe. Her immediate past history showed that she had been in good health and the important fact that, seven days prior to the onset of the present illness, she had visited a coastal town in which there was an epidemic of dengue fever.

Physical examination on admission showed a well nourished and well developed young woman, acutely ill. She was apathetic and totally disinterested in all that went on about her. Her face was flushed and appeared somewhat puffy and the skin was hot and dry. The soft palate and anterior faucial pillars were slightly inflamed, but without membrane, exudate or vesicles. The remainder of the examination was completely negative.

On admission the temperature was 103.6 F., the pulse 98. Urinalysis made immediately on admission was negative. The blood count was as follows: hemoglobin 85 per cent, red blood cells 4,650,000, leukocytes 8,150. The differential

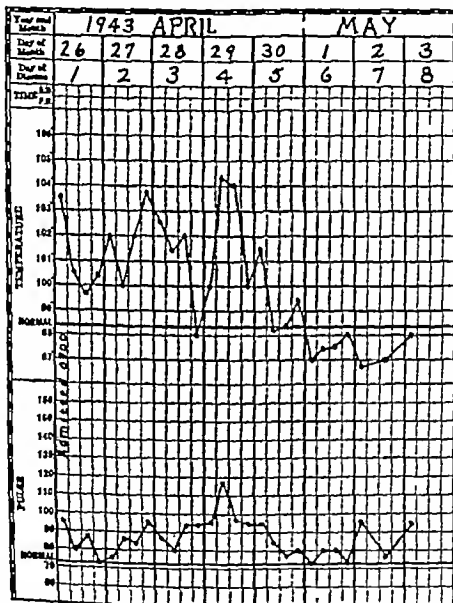


Fig 129 (Case I) —Dengue fever. Illustrates "saddle back" type of temperature with characteristic drop to normal on the third day.

count was: neutrophils 66 per cent, lymphocytes 29 per cent, monocytes 4 per cent, eosinophils 1 per cent.

On the second day of illness, after a brief drop to 100 F., the patient's temperature rose to 103.6 F. in the early evening. She spent a miserable day of generalized aches and the onset of nausea and vomiting. Sedatives most no relief and probably added to her nausea.

On the third day of illness the patient's temperature suddenly normal and the pains left her head, back and limbs. The face lost its flush, her appetite picked up and she was remarkably improved.

By morning of the fourth day the temperature was again elevated. By noon it had reached  $104.2^{\circ}\text{F}$  and the patient was delirious. A tepid sponge lowered the temperature and from this point the fever descended during the fifth day to reach normal on the sixth day of the illness. During the second bout of fever the patient suffered pain of equal severity to that experienced in the first part of her illness. In addition, the lymph glands in the cervical, axillary and inguinal regions were slightly enlarged and painful to the touch. An erythematous rash appeared on the fifth day beginning on the chest and spreading to the abdomen and limbs. It faded as the temperature approached normal. During the height of the fever the rosy blush of palms and soles of the feet appeared, lasting about one day.

Three differential blood counts, done during the illness, were as follows

	First Day	Third Day	Fifth Day
White blood cell count	8,150	4,000	2,700
Neutrophils	66	57	41
Lymphocytes	29	41	52
Monocytes	4	2	3
Eosinophils	1	0	1

Convalescence required about one week with a gradual return of strength. On the ninth day following the onset of the illness there was intense itching of the palms and soles of the feet lasting for two days. No desquamation occurred.

CASE II—A nurse twenty-nine years of age was well until ten days following a visit to the coastal town in which the patient in the first case contracted her illness. At 8:30 in the evening she was suddenly seized with backache, severe enough to necessitate her lying down. In a few hours fever developed with occipital headache and great aching of the legs, arms and bones of the pelvis. In addition she complained of inability to move her eyes because of intense pain.

On admission to the hospital on the following morning her temperature was recorded at  $101.6^{\circ}\text{F}$  and pulse rate 100. She complained of moderate generalized abdominal pain and frequency of urination in addition to those complaints previously mentioned.

Physical examination was negative with the following exceptions. The pharynx was moderately injected and there was moderate tenderness of the entire abdomen, without rigidity or spasm of rectus muscles. The face showed a uniform redness like that of sunburn. The blood pressure was 85/55. Urinalysis showed a slight trace of albumin and 3 to 5 leukocytes per high power field. The initial blood count was hemoglobin 90 per cent, red blood cells 4,010,000, leukocytes 3,900. The differential count was neutrophils 62, lymphocytes 29, monocytes 2, stabs 7.

The primary fever rose to  $102^{\circ}\text{F}$  on the second day, the pulse rate remaining between 100 and 110. On the third day the patient's temperature fell to normal and the pulse rate dropped in proportion. However, before the day had ended, the temperature rose again to  $101^{\circ}\text{F}$  affording her only a momentary respite from the aching back and extremities. It continued to rise to a high point of  $102.6^{\circ}\text{F}$  on the fifth day. At this point a rash, erythematous in character, ap

peared on the extensor surfaces of both forearms, and spread within a day to the thorax, upper abdomen, and back, with great hypersensitivity of the skin

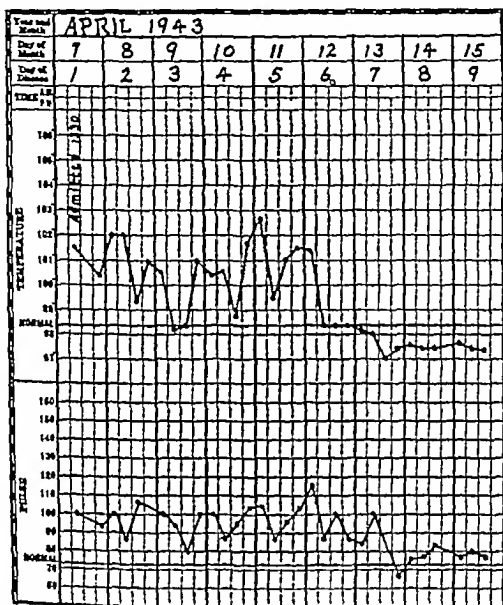


Fig. 130 (Case II) —Dengue fever illustrates less typical febrile response than Case I. The pulse rate is elevated in proportion to the fever

By the following day, as the temperature reached normal, most of the rash had disappeared although a new area on the lower legs and about both internal malleoli was found. The blush of the skin of palms and soles was present, and marked,

	First Day	Seventh Day	Ninth Day
White blood cell count.	3,900	4,400	4,700
Neutrophils	62	49	56
Lymphocytes	29	39	39
Monocytes	2	2	1
Stab cells	7	10	4

and in this instance was associated with moderate generalized itching of the skin of the entire body. There was slight enlargement of the posterior cervical lymph nodes, but no others were affected.



The *differential blood counts* failed to show a progressive reduction of white cells, probably because the second and third counts were done after the acute phases of the illness had passed

*Convalescence* was almost identical with the first case reported, even to the mental depression, the tendency to easy fatigue, and the intense itching of the palms and soles of the feet

### TREATMENT

Except for the relief of pain by means of acetylsalicylic acid or acetophenetidin, and sponging to reduce high fever, there is little that can be done for the patient suffering from dengue. Diarrhea rarely is severe enough to cause much loss of fluid, but profuse sweating together with vomiting will occasionally require the administration of fluids by bowel, or glucose and saline solution by vein. We found barbituric acid sedatives of almost no value in combating insomnia during the acute phases of the diseases. In a few of our cases the pains in the back and extremities so nearly approached in meaning the term "breakbone," that morphine was resorted to, with great success. A single administration of  $\frac{1}{4}$  grain of the sulfate usually relieved the patient's discomfort so that sleep followed naturally. For the aching pain back of the eyes, it was found that a light-weight black cloth, laid across the eyes during daylight hours, or when lights were burning at night, gave considerable relief. The matter of feeding often becomes difficult because of anorexia and it is further complicated, in an occasional case, by a distortion of the sense of taste and smell. In these cases it is advisable to use slightly sweetened fruit juices, being content with small amounts at frequent intervals to avoid vomiting. In the tropics, the delicately flavored water from freshly opened coconuts was found of value.

### PROGNOSIS

The disease is rarely fatal, except in the aged during epidemics, and is almost entirely without complications. One of our patients, a soldier, developed a mild unilateral orchitis. Certain observers have reported rare instances of retinal hemorrhage, ocular palsy and hemorrhage from the bowel, but we encountered none of these.

Deaths from dengue are so rare that no necropsies have been reported, and nothing is known of pathological processes in the disease.

### SUMMARY

- 1 The incubation period of dengue fever in our experience was seven to ten days
- 2 The fever is sudden in onset and lasts six or seven days. It is "saddle-back" in type, the remission occurring on the third day
- 3 The most frequent symptoms are fever, headache, postorbital pain, pain in the back and extremities, and itching of the skin

4 The blood count shows a leukopenia with a relative lymphocytosis.

5 There is an initial erythema of the face at the onset, and later, an erythematous morbilliform rash, beginning on the thorax and extending to the rest of the body and the extremities. When present the rosy blush of the palms and the soles of the feet is followed in three to four days by intense itching.

6 The diagnosis is largely a clinical one. The postorbital pain is especially characteristic and is aggravated by any ocular movement. The fever is characterized by a sudden elevation with a drop on the third day. A secondary rise occurs, to reach a peak equal to or above the initial fever, with a rapid return to normal on the sixth or seventh day.

7 Complications are very rare. In uncomplicated form the disease is not fatal.

8 Prevention consists in eradication of the vector *Aedes aegypti*, and in the screening of all patients with the disease. For troops in the field the use of protective clothing, repellent, and mosquito bars are important considerations.

9 Treatment is entirely symptomatic.

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# THE MILITARY ASPECTS OF LEPROSY

MAJOR WILLIAM U McCLENAHAN

MEDICAL CORPS, ARMY OF THE UNITED STATES

THE presence of troops in areas where leprosy is endemic presents a new problem to the medical officer in the field. The fact that the signs and symptoms of this disease may appear years after the initial contact may present a similar problem to civilian physicians in the future.

No attempt will be made to discuss the etiology, pathology, physiology, or treatment of leprosy. The complexity of this subject can be appreciated by considering briefly the following facts. Although it is one of the oldest, most widespread and dreaded diseases of mankind, Frazier has stated that, "It may be said without serious risk of contradiction that less is known of the essential factors in the pathogenesis and transmission of leprosy than of the other great infectious diseases of mankind." This statement is even more significant when compared with the remarkable advance made in the knowledge of tuberculosis. Although Koch announced the identity of the bacillus of tuberculosis in 1882, Hansen in 1874 reported finding a bacillus which he considered as the probable etiologic factor in leprosy. Since this discovery, however, the Hansen bacillus has not yet with certainty been cultivated on artificial media and the disease has never yet been established in progressive form in laboratory animals.

The peculiar behavior of this disease is also shown by its rarity in our large cities at the crossroads of world travel, where conditions might be considered favorable for its introduction. McCoy of the public health service of New York City states, "With a single exception I have been unable to find any record that any one has ever been infected with leprosy in New York City, although in the aggregate over a period of a few decades, literally hundreds of lepers have been domiciled there for various periods of time." On the other hand, leprosy was introduced into Hawaii about 1854, reached its maximum prevalence in 1894, has since then shown a slow decline but from 50 to 100 cases are still reported each year. In the island where this hospital was first stationed, leprosy was introduced in the latter part of the last century and 5000 cases were reported within a few years. One of the four European nuns in charge of the local leprosarium had contracted the disease after eight years of exposure.

## EXPERIENCE IN A MILITARY HOSPITAL LOCATED IN AN ENDEMIC AREA

We should like to discuss briefly how this problem was handled in an Army field hospital in a country where leprosy was endemic both

among the native and white populations. A memorandum was sent out by the division surgeon to all medical officers of his command, recommending that local civilian and military physicians should be consulted in any case of suspected leprosy. They had all had special training in this disease plus years of experience in its diagnosis and treatment. Our consultations with them were very satisfactory and their opinions were most helpful. This memorandum also contained a brief review of the signs and symptoms of the disease, as well as a description of the laboratory technic for obtaining, staining and identifying the Hansen bacillus from nasal smears.

Because of the isolated location of the hospital, mingling of soldiers with the local rural population was natural. The laundry facilities, poor to say the least, tempted a soldier, with money in pocket and nowhere to spend it, to turn this chore to more than willing civilians. To meet these situations the hospital command organized a course of lectures on the subject of leprosy. The entire personnel attended these lectures. The names and addresses of lepers and suspects were obtained from the local civilian authorities. This information was posted and the areas placed off limits to troops. Special attention was drawn to the dangers of having laundry done in the homes of families where leprosy was suspected. Nonmilitary admissions to the hospital were restricted to civilians in the employ of the U S Armed Forces, ones injured by military vehicles, cases of serious emergencies where local medical help was not present, and cases referred by civilian physicians after being approved by proper Army authorities. Separate wards were equipped and provided for these civilians, their bedding and eating utensils were kept separate, and they were not allowed to eat in the mess line. Transfer to civil hospitals was made as soon as possible, especially in suspected contagious cases. It is also right to assume that the strict public health measures carried on in all military installations did in themselves offer some safeguard.

#### CASE REPORTS

The following case reports illustrate the clinical manifestations of early and late leprosy.

**CASE I**—A white female child nine years old who had been born and raised on the island, was admitted for study. She had been referred to us by a U S Army Station Hospital to which her grandmother prompted by the appearance of a rash and the memory of a former native maid in the home who had developed leprosy, had taken her. The child's contact with this servant had been for about six months' duration four years previously. The patient's chief complaints were a bluish discoloration of both cheeks and a "lump" on thigh.

**History of Present Illness**—Five months before admission a noted on the anterior portion of the right thigh. It was started as an irregularly shaped, tender pruritic swelling with a rounded by a bluish margin. It had never bled or discharged. D

month the swelling had subsided, tenderness had disappeared and the pruritus was only occasionally present

Approximately one week after the onset of this lesion the child developed the bluish patches on both cheeks (The grandmother had not noted or had disregarded the lesions on the extremities described later) The girl had been in perfect health otherwise There had been no apparent weight loss, anorexia, or increased fatigue However, on severe exertion her right leg "tended to feel crampy and heavy"

*Birth History*—The delivery had been normal The birth weight 8 pounds 13 ounces, (4 kg) and the child had been breast fed until she was ten months of age Raw milk had been used in infancy (It is interesting to note in this connection that the head of a large, government-inspected meat packing plant in the island reported to us that no case of bovine tuberculosis had been found since its establishment several years previously) The patient's physical development had been entirely normal She was highly emotional and had frequent temper tantrums

*Past Medical History*—With the exception of measles no other contagious disease had been incurred Worms had at one time been discovered in the stools (Intestinal parasites were endemic on this island)

*Family History*—The patient was an illegitimate child who had lived with her grandmother since birth Both parents were living and well and her mother had had three normal children by a different partner with no history of miscarriages and stillbirths There was no knowledge of tuberculosis, syphilis or leprosy in the family

*Physical Examination*—The patient was a well developed and well nourished, white, female child whose body build and mental development were consistent with her actual age. She showed the following significant findings The nasal mucous membranes were moderately congested and covered with a slight opalescent mucoid discharge which was also seen in the posterior pharynx. Except for a few small, tender anterior cervical glands, there was no other lymphadenopathy The spleen was not palpable The skin was definitely mottled over the upper and lower extremities On each cheek was a pale, bluish macular patch whose periphery was reddish and whose center was pale in color Sensory perception for temperature, pain and touch had not apparently changed in these two areas The skin did not appear to be thickened On the arms and thighs there were several small, circumscribed macular areas averaging 15 cm in diameter, pale in color with diminished sensory perception to temperature, pain and touch On the right midthigh there was an area approximately 5 by 8 cm in size, tawny in color, covered with a rough, scaly surface Over this lesion pain, thermal and tactile sensation showed marked impairment No thickening of the superficial nerves of the extremities could be detected and there was no sensory change noted, except in the area involved Patellar and Achilles reflexes in the left leg appeared to be slightly increased The Babinski, Kernig and Romberg tests were negative No ankle clonus was present and the patient walked normally No wasting of the muscles or motor weakness could be detected in any extremity

*Laboratory Studies*—Blood count Hemoglobin 90 per cent, red blood cells 4,010,000, leukocytes 5750 with a differential count, neutrophils 67, lymphocytes 19, eosinophils 7, basophils 1, stab cells 2, monocytes 4 The urinalysis and Kahn tests were negative Three smears obtained by means of cotton applicators were negative for acid-fast bacilli Material obtained by scraping the upper portion of

the nasal septum with a dull curet, without drawing blood was found to contain acid fast bacilli on each examination done for three successive days. The bacilli were rod-shaped and occasionally found in clumps.

A diagnosis of early leprosy was made on the basis of the history, physical findings and laboratory studies. The cutaneous diseases considered in the differential diagnosis were tuberculosis, syphilis and leukoderma. Favoring the diagnosis of leprosy were the following facts

1 The child had lived her entire life in a country where leprosy was endemic. (The great susceptibility of children to this disease is universally recognized)

2 There was a history of exposure in early infancy so suggestive that her grandmother brought her for study with this disease in mind.

3 The signs and symptoms were limited to skin and nerve involvement. The cutaneous lesions showed sensory changes not found in the above diseases

4 The location and appearance of the cutaneous lesions were similar to those frequently seen in leprosy

5 The blood Kahn test was negative.

6 Acid-fast bacilli with the morphology of the *Bacillus leprae* were isolated from scrapings of the nasal mucous membrane.

Case II.—The patient's age and debility as well as linguistic difficulties made the history inadequate. He was a seventy-two-year-old white civilian who migrated to the island in 1892. His chief complaints all centered on his gastro-intestinal tract. They consisted of severe rectal pain associated with frequent small bowel movements, a sense of incomplete bowel evacuation and hemorrhoids. Loss of weight and strength were marked. These symptoms had been present for three years prior to admission. For thirty years he had suffered from bronchial asthma. The diagnosis of rectal carcinoma was made but no biopsy was taken.

During the course of the physical examination a definite cutaneous thickening about the nose and cheeks was observed. Several, round, macular, white lesions were present on the external aspect of the left leg. In these areas anesthesia was present. The superficial nerves of the left leg below the knee were palpable. Almost complete anesthesia was found on the mesial half of the dorsum of the left foot. No motor weakness of the lower extremities was present, and the knee jerks were active and equal. Three nasal smears taken with cotton tipped applicators were negative for the acid fast bacillus of Hansen. In view of the signs the diagnosis of leprosy advanced stage, was made and was confirmed by a civilian physician. He was transferred immediately to a local hospital.

#### EARLY CLINICAL MANIFESTATIONS AND DIAGNOSIS

Incubation Period and Onset—The incubation period varies greatly. The generally accepted time is from one to five years. The early manifestations are vague and indefinite, consisting of numbness, weakness and mental depression. The onset is often

insidious, as in the first case described, that the cutaneous lesion is the first symptom noted

**Cutaneous Lesions—Early Stage**—In a typical case these macular lesions are usually multiple. They are at first erythematous, with the appearance of limited areas of sunburn. Their size is variable, the lesions being from 1 or 2 mm to several centimeters in diameter. They increase by peripheral extension. Often these macules become pigmented and thickened. The lobes of the ears and the face are the areas of predilection, although the extensor surface of the forearm, thighs and buttocks are favorite sites for the indurated lesion. Muir, in studying the first appearance of lesions of the skin of 1056 lepers in India, found the early lesions to be present first on the cheeks and outer surfaces of the extremities. The palms of the hands, soles of the feet, hairy scalp, groin and axillary regions are almost never involved. At first hyperesthetic, the cutaneous lesions soon show the loss of pain, thermal and sensory perceptions. Another quite characteristic sign is that the spots remain dry even with a generalized perspiration.

**Cutaneous Lesions—Intermediate and Late Stages**—The second important stage may be described as that of skin thickening and subcutaneous nodule formation, which usually are seen on particular body areas. Stitt points out that one should always palpate the lobes of the ears and eyebrows for shotlike nodules. As the disease progresses, the facial lesions cause a depilation of the eyebrows and beard. The skin over the nose and cheeks becomes indurated causing a smoothed-out, masklike expression. In extreme cases the leonine facies is produced, so characteristic of nodular leprosy. The mucous membranes of the mouth, nasopharynx and larynx are frequently involved. In fact, authorities agree that practically every leprosy patient has some nasal lesion. Del Rio (1936) found the nose affected in 82 per cent of all cases. Ulceration may follow, with disfiguring and debilitating scar formation as the lesions heal.

**Nervous System Involvement**—After the cutaneous changes, the most common early symptoms are caused by nervous system involvement. Attention has already been called to the anesthesia of the skin patches. Various manifestations of neuritis are frequent. Nerve irritation causes neuralgic pains or signs of sensory disturbances in the areas supplied. The nerve may become uniformly thickened to three or four times its normal size, or it may be slightly enlarged, or nodular like the beads of a rosary. The affected nerves are rarely detected above the knee or elbow and are naturally most readily palpated where subcutaneous. The ulnar, anterior tibial, peroneal and facial nerves are the most frequently involved. As this neuritis becomes more advanced, trophic changes in the skin, nails, muscles and bones result. Such changes are most commonly seen on the fingers and toes. The optic, olfactory and auditory nerves are seldom involved. The lymphatic glands, which drain the affected parts, enlarge but rarely suppurate. As one would

suppose, the cervical, epitrochlear and inguinal glands are most often enlarged

**Laboratory Diagnosis.**—In any suspicious case, careful laboratory tests are imperative. In from 50 to 80 per cent of cases of leprosy the *Bacillus leprae* can be found in smears of the nasal mucosa, secured with a dull curet without drawing blood. Smears taken with cotton applicators were found unsatisfactory. If any cutaneous macule, papule, or nodule is present, a small incision should be made through the epidermis well into the corium. The serous exudate thus obtained should then be smeared on a slide for microscopic examination. Acid-fast bacilli are usually found with ease and in great numbers in the nodular lesions and less frequently in the erythematous patches of flat infiltrations. The Ziehl-Neelsen-Gabbett carbolfuchsin solution, as used for staining tubercle bacilli, gives the most satisfactory results.

**Mental Effects.**—It would be unwise to close this discussion without mentioning the mental effect that the fear of leprosy may produce in some of the troops stationed where the disease is endemic.

A soldier, whose military record and mental ability were so good that he was recommended for officers' candidate school, noted a slight swelling beneath the skin on the lower mesial aspect of the right arm. He immediately became obsessed with the idea that he had leprosy, with resulting mental panic and emotional distress. All reassurance from surgeons and physicians failed. The lump was excised and found to be a typical lipoma as had been anticipated before operation. He was shown the tissue removed but his phobia continued. Only time and the comfort from religion have apparently removed this fear. The mental trauma, however, has so affected his personality that promotion is now out of the question and his military efficiency is permanently impaired.

It is the duty of the Army physician to relieve such anxiety in soldiers stationed in areas where leprosy is endemic. To the civilian physician falls the responsibility of preventing unnecessary worry in the families of these soldiers.



# PRIMARY ATYPICAL PNEUMONIA AS SEEN IN THE TROPICS

CAPTAIN HARLAN F HAINES AND CAPTAIN CLARK M FORCEY

MEDICAL CORPS, ARMY OF THE UNITED STATES

DURING the past decade there have been many reports in the literature describing a benign nonbacterial pulmonary disease in young adults. In 1934, Gallagher<sup>1</sup> described an epidemic of this disease in New England and almost simultaneously Bowen<sup>2</sup> reported a form of pneumonitis occurring in white troops in Hawaii. Clinically the diseases were very similar. Since then a number of observers have added to the knowledge of the disease, among them Reimann,<sup>3</sup> Longcope,<sup>4</sup> Stokes et al,<sup>5</sup> Eaton et al,<sup>6</sup> Campbell et al,<sup>7</sup> and Dingle et al.<sup>8</sup> This newly recognized entity has been known by various names. The Army has designated it as "primary atypical pneumonia, etiology unknown."

The most thorough investigation of this syndrome to date has been the studies done under the auspices of the Commission for the Investigation of Atypical Pneumonia and Other Respiratory Diseases<sup>9</sup> during the summer of 1941 when a high incidence of "atypical" pneumonia was observed at Camp Claiborne, Louisiana. The methods of study were based on a combination of three approaches to the problem: clinical, epidemiologic and etiologic. The results of the clinical studies were in general agreement with observations of other investigators. It revealed that the disease was characterized by a mild to moderately severe illness of gradual onset in which fever, headache, malaise and chilliness without rigor predominated over symptoms usually referable to the respiratory tract in early stages. A most characteristic feature of the syndrome was the late development and paucity of physical signs in contrast to the definite roentgen-ray evidence of the disease. However, by the time the patients were admitted to the hospital the cough was productive in two thirds of the cases. Although almost all the patients were febrile on admission, the pulse and respiratory rates were low. The most characteristic finding on physical examination of the chest was subcrepitant and sticky rales best elicited by cough and deep breathing. Dullness, abnormal breath or voice sounds, pleural friction rub and differences of excursion of the chest were the exception.

In comparison to these relatively slight physical findings, the extent of pulmonary infiltration as shown by roentgenogram was striking. Characteristically at first, there was a unilateral or bilateral increase in the hilar shadows. Perihilar infiltration became increasingly evident in subsequent plates and the shadow then extended toward the periphery of the pulmonary field either in a wedge- or fan-shaped

shadow. This usually faded before the periphery was reached. Only rarely was an entire lobe involved. A common site for the lesion was one or the other cardiophrenic angle. The degree of progressive change of the lesions over a period of a few days was one of the more striking features. Usually the lesion progressed as described and then underwent slow resolution over a period of one to three weeks. The enlarged hilar shadows and increased pulmonary markings occasionally persisted for several weeks.

Laboratory data revealed an essentially normal leukocyte count in the febrile and afebrile stages of the disease. Although occasionally there was an increase in the leukocyte count as the disease progressed, the changes could not be correlated with the clinical severity of the disease or changes in bacterial flora.

The etiologic and epidemiologic investigation of the Commission comprised an important part of their study. Search for some bacterium, fungus, Rickettsia or virus as a cause of atypical pneumonia yielded no positive results. It was believed that some new agent, probably a virus, was the etiologic factor. The epidemiologic studies were concerned with the communicability, mode of spread and possible relation to other illnesses affecting the respiratory tract. The observations were consistent with the hypothesis that unrecognized and inapparent infections constitute a reservoir for the etiologic agent and that the disease is probably transmitted by contact from person to person.

Roentgenograms have been found of great value in the diagnosis and study of primary atypical pneumonia by all investigators. Campbell and his associates<sup>7</sup> studied the roentgenologic aspects of 200 cases. They described the shadows present as conforming to the general distribution of the bronchi. Superimposed on a stringy density was a mottled type of shadow which occurred in any part of the chest but was most often seen at the right cardiophrenic angle at or below the lung roots or along the left border of the heart. As the result of the x-ray findings and one postmortem they concluded that the pathological changes of atypical pneumonia are most likely a bronchiolitis, peribronchitis and peribronchiolitis with associated areas of atelectasis rather than a true pneumonia. In 11 per cent of their cases apical lesions were present which could easily have been confused with tuberculosis on one x-ray examination.

#### PRIMARY ATYPICAL PNEUMONIA AS SEEN AMONG ARMY PERSONS ON A SOUTH PACIFIC ISLAND

While stationed on an island in the South Pacific Area, it was a privilege to observe some forty cases of primary atypical pneumonia occurring among white American soldiers stationed there in 1947. A larger percentage of these patients exhibited the characteristic picture previously ascribed to this disease. The majority of the

sonnel which composed the task force came from the New England states while others came directly from Louisiana. About one month prior to embarkation for overseas duty the New England troops returned from Carolina, to their post in New England. Within the following week several hundred were admitted to hospitals with upper respiratory infections. On a small number of these a diagnosis of atypical pneumonia was made. In late January, the force left the United States. They lived under crowded conditions on the transports. Many officers, nurses and large numbers of soldiers had upper respiratory infections during this voyage but to our knowledge a diagnosis of pneumonia was not made. Roentgenograms were not available for the study of these cases.

The first patient which we observed with primary atypical pneumonia was seen just at the time of our arrival at our final destination and approximately seven weeks after leaving the United States. It is unlikely that the incubation period is that long. Subsequently several cases were seen within a short period, and during the next three months we admitted most of the patients whom we have seen with this disease.

**Symptoms**—The onset of the disease was gradual, with mild prodromal symptoms for two or three days in most of the patients. Chilliness was common but frank chills were unusual. Soreness of the throat was present in nearly half of the cases. Headache was very frequent and malaise almost universal but prostration was not marked. Cough appeared as an early symptom and was often distressing, being frequently paroxysmal and usually nonproductive for the first few days. Sputum was scant, mucoid and not rusty. Occasional blood-streaked specimens were noted. Herpes was not seen. None of our patients had a coincident acute pleurisy.

**Physical Signs**—The temperature seldom rose above 103° F but there was considerable daily variation. The pulse rate was little elevated and the respirations only slightly increased. Cyanosis was never more than a slight duskeness of the lips. There was usually some pharyngeal irritation, although this was mild. Physical signs over the chest were often minimal and usually appeared late. There was seldom more than a slight change to percussion. Suppression of breath sounds was usually the first sign and fine crackling rales at the end of inspiration were early findings in many cases. As the patient improved clinically, the physical signs often increased. A shifting of the signs from one area to another was not uncommon. Persistence of rales into convalescence was seen in several patients who had apparently made a complete recovery.

**Laboratory Studies**—The common laboratory studies were essentially negative in our patients. The white blood counts and differential counts were within the limit of normal in practically every case. Sputum cultures were not available but smears of the sputum showed

no predominant organisms except in one case. In this patient, who became seriously ill, gram positive diplococci were consistently present after the first week. These could not be typed. It was thought that a complicating pneumococcic pneumonia was present in this case in which recovery ensued by crisis after a stormy and prolonged course.

**X-ray Findings**—The x-ray findings on these cases nearly always showed the lesion to be of greater extent than physical examination would lead one to believe. This, of course has been emphasized by all writers on the subject. Postero-anterior films were taken on all patients and in addition left anterior oblique exposures were taken on those patients with suggestive signs in the left lower lobe. Several lesions that were hidden almost entirely by the heart shadow on the postero-anterior view were seen on the left anterior oblique films. The films showed slight involvement of the parenchyma along the bronchioles with a spotty increased density at the terminal ends of the bronchioles. In a few cases a majority of the lower lobe bronchioles were involved and the x-ray shadows suggested peribronchiolar parenchymal lung changes. Resolution, as seen in the usual case of lobar or lobular pneumonia, did not occur. In most cases there was little improvement in the x-ray appearance for about two weeks. Thereafter there was usually a gradual clearing of the process but this was not always complete. The residual changes though slight, suggested a fibrosis. Two patients, x-rayed six months after clinical recovery, showed residual lesions which suggested peribronchiolar fibrosis. Lesions of the upper lobe may show findings resembling those seen in tuberculosis, and in patients in whom the process cleared slowly, definite differentiation from an acid-fast infection was not possible by x rays alone.

**Course of the Disease**.—The course of the disease was usually mild. In most cases the temperature fell to normal by lysis in four to eight days. In a few, slight fever persisted as long as two weeks. The cough was apt to be very persistent and frequently lasted long after the acute phase of the disease. It was sometimes possible to hear fine crackling rales over the area of the lesion for as long as eighteen or twenty days after the onset of the illness. In a few cases, <sup>v</sup> <sup>f</sup> was protracted as evidenced by easy fatigability. There <sup>v</sup> in our series and only one patient was dangerously ill.

**Treatment**.—Treatment was symptomatic. For relief of pain in full doses was necessary and occasionally morphine secure rest at night. The sulfonamides were tried in a few cases but were soon discontinued.

#### REPORT OF A CASE

A soldier, aged twenty-eight years, was admitted to the hospital of fever, chilliness, general malaise and anorexia. Shortly after

island and one week prior to admission he had developed a "slight cold." During a long trip in an open truck he developed generalized aches, malaise, anorexia, weakness and severe headache. He noticed a slight hacking cough and he had alternating bouts of chilliness followed by fever. Upon arrival at his destination he was admitted to the hospital acutely ill.

The principal physical finding on admission was a few crackling rales at the right base. The temperature was 103° F with a pulse rate of 108 and respiratory rate of 28. The following morning the patient felt improved and his temperature was nearly normal. Physical examination of the chest revealed only a few fine rales at the right base on deep inspiration and a slight suppression of breath sounds over this area. The temperature was again elevated later in the day and the general symptoms returned. Cough had increased but no sputum was present. Facilities for x-ray examination of the chest were not available at this time.

During the next few days fever persisted, reaching 102° F several times, but the patient did not feel or look particularly ill. Four days after admission, physical examination revealed slight dullness to percussion at the base of the left lung posteriorly, with fine, crackling rales and a few similar rales at the right apex. Cough had persisted and was accompanied by some substernal distress. A study of the sputum revealed no tubercle bacilli or predominant organisms.

During the next two weeks, the patient improved gradually, but a dry cough and slight evening elevation of temperature persisted. Sputum was scant and mucoid in type. An x-ray of the lungs on April 12, 1942, approximately two weeks after admission, revealed a marked increase in trunk shadows and an area of increased density lateral and slightly above the right hilum. This had the appearance of a resolving pneumonia. Lateral or oblique x-rays were not taken. Four days later a repeat x-ray showed no change. At the end of three weeks there was an occasional slight elevation of temperature and some cough persisted. An occasional rale was heard at the left base posteriorly.

After one month of hospitalization the patient looked well but occasional rales were heard at either base. Cough was less pronounced but was still present. The patient was discharged to light duty after thirty-eight days of hospitalization with a slight, dry, hacking cough still present. A roentgenogram at this time revealed little change from the original film.

Several leukocyte counts made during the course of the disease were within normal limits, and repeated sputum examinations for pneumococci and acid-fast bacilli were negative. The corrected sedimentation rate the day before discharge was 10 mm in one hour.

The patient was seen occasionally on sick call during the next four months because of a slight but persistent dry cough. The physical signs over the lungs cleared completely a short time after he left the hospital. A check-up x-ray examination in July, 1943, approximately fifteen months after the illness, revealed the following: "There is thickening of the interlobar pleura on the right side. There is slight scarring throughout both lung fields. The trunk shadows are markedly increased. No active parenchymal lung change is seen. The heart is not enlarged transversely."

This case of primary atypical pneumonia illustrates the mild general symptoms, severe cough and the paucity of physical signs in the average patient with this illness. There were no significant findings in

any of the usual laboratory studies. Convalescence was slow as evidenced by persistent cough, slight temperature elevation and slow disappearance of rales. The x-ray findings were a definite aid in diagnosis and in following the course of the disease. Slight but permanent residual lung changes are suggested in this case by the x-ray taken several months after clinical recovery.

#### COMMENT

It is of interest that during the first six months overseas, 4 per cent of our total hospital admissions were for atypical pneumonia, while one year later, during the same period of time, we saw only one case of atypical pneumonia in over 2000 admissions. In addition, our rate for admissions for all respiratory diseases had diminished greatly. These findings are conceivably due to living in the open air and coming in contact with relatively few people from outside the immediate area.

Additional experience with civilians and native troops in the area where we were stationed may be of significance. Nearly every year an epidemic of "la grippe" spreads through the island. We examined several of the white population with this condition and concluded that their symptoms and findings were consistent with influenza. One group of fifty native scouts, attached to and intimately associated with an American Army battalion, were hospitalized nearly en masse with a severe "grippe." A diagnosis of atypical pneumonia was substantiated in eight of these patients. We are unable to say whether a small percentage of the white population with "la grippe" who had slight contact with our Army also developed atypical pneumonia. It was thought the native troops probably acquired their infection from our soldiers.

#### SUMMARY

- 1 Forty cases of primary atypical pneumonia were observed among American troops on a small island in the South Pacific.
- 2 The disease was mild and the findings comparable to those of other authors. There were no deaths.
- 3 The etiologic agent may have been carried from the United States during the epidemic of 1941-1942.
- 4 The great decrease in incidence of this disease over a period of two years is probably due to several factors. Living in the open in a tropical climate and lack of contact with troops recently arrived from the Northern Hemisphere are probably of prime importance.
- 5 X-ray studies are of great aid in the diagnosis of atypical pneumonia. With the involvement of an upper lobe, radiologic signs may be confused with tuberculosis. Residual suggestive of peribronchiolar fibrosis, may be present after clinical recovery from this disease.

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## THE DYSENTERIES

CAPTAIN JOHN J. CALARCO

MEDICAL CORPS, ARMY OF THE UNITED STATES

Dysentery is an important problem in the armed forces. Prevention of epidemics of dysentery is essential if the efficiency of troops is to be preserved. Most of the epidemics of this disease occur shortly after setting up new bivouac areas or under conditions in which ordinary sanitation is impossible. The more difficult the sanitary problem the more likely the disease is to appear. Of the two principal types of dysentery, bacillary and protozoal (amebic), bacillary dysentery is the more important from the military standpoint. In temperate climates the disease is more common in the summer months, but in the tropics it occurs at any time. We had the opportunity in a large hospital in the South and Southwest Pacific theaters to treat both types of dysentery.

### ETIOLOGY

Dysentery is a term denoting a symptom complex characterized by inflammation of the intestines and attended by pain in the abdomen, tenesmus and frequent stools containing blood and mucus. In the South and Southwest Pacific area dysentery in soldiers has been due to both bacterial and protozoal (amebic) infection. Bacillary dysentery is caused by *Shigella dysenteriae*, which is a gram-negative, non-motile coliform bacillus. There are several distinct serological strains of the bacillus, and endemic and epidemic cases are seen with all types. Protozoal (amebic) dysentery is caused by the *Endamoeba histolytica*, a polymorphic, protoplasmic single cell organism found in the feces in both vegetative and encysted forms.

### EPIDEMIOLOGY

The transmission of dysentery by water and food handlers has long been recognized and fully appreciated by military authorities. It has been our experience that the most important vector of bacillary dysentery in the tropics is the common fly. Wherever bivouac areas are established, flies gather in hoards.

When dysentery broke out among American troops who had just arrived on a South Pacific island, a commission was established to investigate the problem. After field surveys and a review of the clinical histories of patients admitted to the hospital with dysentery, the conclusion was reached that the outbreak was due to the lack of application of the principles of field sanitation. Open latrines (straddle trenches), unscreened kitchens and mess halls were all in close proximity to each other in the organizations where dysentery was reported.



The fact that patients had intestinal myiasis (fly larvae in feces) proved the gross contamination of food by flies. As sanitary discipline was established and logistics improved, the number of hospital admissions for dysentery decreased rapidly. Over a period of fourteen months, similar but smaller outbreaks were observed in newly arrived troops. When sanitary regulations were rigidly enforced, the disease became sporadic. In contrast, at a later date, when experienced troops landed on a previously unoccupied island, the incidence of bacillary dysentery was negligible due to the availability and immediate use of latrine boxes and screening, and the rigid enforcement of the principles of field sanitation.

A small outbreak of amebic dysentery in one organization was traced to the improper treatment of water. In another series of sporadic cases of this type of dysentery, patients all gave a history of eating fresh, uncooked vegetables or fruits from native establishments.

#### CLINICAL MANIFESTATIONS

**Bacillary Dysentery.**—The usual case of bacillary dysentery was characterized by prodromal symptoms consisting of headache, malaise, anorexia, and occasionally nausea and vomiting. Fever was usually present, the temperature occasionally rising to 104° F or above during the first few days. Chilliness or even a frank chill was not uncommon. Abdominal cramps became manifest early, followed by diarrhea within twenty-four to forty-eight hours. In severe cases prostration was marked, and occasionally delirium was present.

In those patients whose diarrhea appeared late the diagnosis was often confusing. These cases, if mild, usually improved rapidly after a few loose bowel movements. In severely ill patients, cramps and tenesmus were marked, the stools numbered twenty to forty a day and were composed largely of small amounts of bloody mucus. Physical findings usually revealed generalized tenderness of the abdomen, particularly over the course of the large bowel. Increased peristalsis was heard by auscultation.

The following case history is representative of the average case of bacillary dysentery which we observed.

**CASE I**—A thirty-four-year-old soldier was hospitalized on December 2, 1942, because of diarrhea. He had been in good health until about thirty-six hours prior to admission, when he noted a chill associated with nausea and vomiting. This was followed by abdominal cramps and several loose, watery stools. History revealed that flies were prevalent at his camp and that open latrines (straddle trenches) and unscreened kitchens were being used. The patient also stated that other members of the immediate command were suffering from diarrhea. There was no previous history of dysentery and the personal, family and systemic history was noncontributory.

Physical examination revealed moderate tenderness over the left lower quadrant of the abdomen, associated with pain. The temperature was 102° F the pulse

rate 76 and respirations 20. The remainder of the examination was essentially negative.

The patient's temperature returned to normal within thirty six hours and remained so. He averaged six to ten liquid, grossly bloody stools for each of the first four days. The number of stools then dropped to a daily average of four. Forty-eight hours later the stools were normal. Sigmoidoscopic examination on the third hospital day revealed diffuse injection of the rectal mucosa, mucus, and small areas of yellow red exudate. No ulceration or hemorrhagic areas were noted.

The patient was given a liquid diet for the first five days and confined to bed. The diet was gradually increased to include soft foods as the stools lessened in number. He was given a regular diet on the seventh day. Phenobarbital and tincture of belladonna were administered during the first five days. He was returned to duty December 15, 1942, fully recovered.

**Laboratory Studies**—Blood study on December 3, 1942, gave the following results: red blood cells 3,740,000, hemoglobin 70 per cent, leukocytes 8900. Differential count: neutrophils 62, lymphocytes 26, eosinophils 3, basophils 1, stab cells 3, and monocytes 5. A urinalysis was negative. Stool examinations on December 3 showed a few red blood cells and many pus cells. No amebae or ova were seen. Stool culture on December 5 revealed organisms of the *B. coli* aerogenes group. Stool examination repeated the following day showed no essential changes. On December 11 the stool was normal.

**Comment**—This case is representative of the mild bacillary dysenteries seen in soldiers shortly after their arrival at new bivouac areas. Patients who were hospitalized early in the course of their illness and placed at complete bed rest had less morbidity and few complications. Chronic, recurrent, low grade bacillary dysentery, proctitis and cryptitis were the chief sequelae observed. The average case of this type did not require sulfonamide therapy, the patient recovering rapidly on symptomatic treatment. Bed rest, controlled diet, sedation and antispasmodics were the chief measures employed.

**Amebic Dysentery**—The typical case of amebic dysentery was characterized by an insidious onset, irregular diarrhea and a feeling of abdominal uneasiness or dull griping pains. A normal temperature or low grade fever was the usual finding. In most patients general symptoms were not striking and they were frequently ambulatory until just before admission to the hospital. The stools characteristically consisted of semisolid to liquid brown fecal material, foul smelling, and intermingled with blood and mucus in varying amounts. At times the stools consisted of small dejecta of bloody mucus with little fecal material.

The following case history is representative

**Case II**—A twenty-eight year-old soldier entered the hospital on March 31, 1943, with a history of six to ten bowel movements daily for the past week, associated with abdominal cramps. The bowel movements were watery in character and he had noted blood clots in his stools. There had been no fever, anorexia, nausea or other symptoms. He had attended sick call daily but the medication

received did not improve his condition. There was no previous history of dysentery and his personal, family and systemic histories were noncontributory.

Physical examination revealed tenderness over the left lower quadrant of the abdomen and very active peristalsis. The temperature was 98.6° F., the pulse rate 80 and respirations 20. The remainder of the physical examination was essentially negative.

The patient was afebrile during the period of hospitalization. He was given a soft bland diet and symptomatic treatment. During the first seven days after admission he averaged four liquid stools daily. These were grossly bloody and were associated with some mucus. Sigmoidoscopic examination on the third hospital day revealed a diffusely injected lower bowel without ulceration. The patient was given sulfaguanidine, the initial dose being 4 gm followed by 1 gm. every four hours. No improvement was noted during the next few days. On April 7, stool examination showed many vegetative forms of the *Endamoeba histolytica*. A sigmoidoscopic examination made the same day revealed a diffusely injected mucosa with pinpoint ulcerations. Mucus and blood were present. The examination had to be discontinued because of pain and tenesmus.

The sulfaguanidine was discontinued and emetine hydrochloride therapy was begun. The drug was injected intramuscularly once daily, the initial dose being 0.032 gm ( $\frac{1}{2}$  grain), the second dose 0.064 gm (1 grain), and the third and succeeding doses 0.10 gm ( $1\frac{1}{2}$  grains). This therapy was continued for eight days. Coincident with the emetine hydrochloride, the patient received chiniofon (7-iodo-8-hydroxyquinoline-5-sulfonic acid 80 per cent with sodium bicarbonate 20 per cent) orally, 1 gm daily, in divided dosage. Steady improvement was noted. Muscular soreness developed at the site of the injections. The stools were reduced to one formed stool daily. Occasionally traces of blood and mucus were present. Following the completion of the course of emetine hydrochloride and chiniofon, the patient was given sulfaguanidine for four days, at the end of which there were no further symptoms. The muscular soreness disappeared gradually and he was returned to duty May 3, 1943. Three stool examinations were negative for amebae before discharge.

**Laboratory Studies**—Blood count on April 2: red blood cells 4,730,000, hemoglobin 90 per cent, leukocytes 6250. Differential count: neutrophils 68, lymphocytes 23, monocytes 5, stab cells 4. Urinalysis: several specimens showed no abnormalities. Daily examinations of the stools revealed blood and mucus. In addition the specimens of April 7 and 9 showed many vegetative forms of *Endamoeba histolytica*. On April 13 encysted forms of the *Endamoeba histolytica* were found. Several stool examinations after April 27 were entirely normal.

**Comment**—The diagnosis was in doubt when this patient was first seen. The lack of fever and the presence of low grade diarrhea with abdominal cramps unassociated with general symptoms were suggestive of amebic infection. The diffusely injected mucosa with pinpoint ulcerations on sigmoidoscopic examination, with the initial failure to find amebas, was against this diagnosis. Later, the finding of both forms of the *Endamoeba histolytica*, with the therapeutic response and afebrile course, made the diagnosis of amebic dysentery quite definite. Superimposed secondary infection was no doubt a factor in the sigmoidoscopic findings.

Bacillary and Amebic Dysentery in the Samo Patient—Occasionally bacillary and amebic dysentery were combined in the same patient. When this occurred the diagnosis was often difficult and response to treatment was slow. The following case illustrates this type of problem.

CASE III—A twenty three year-old soldier entered the hospital on January 18, 1943. His present illness began about December 12, 1942, with diarrhea associated with abdominal cramps and fever. He was admitted to another hospital on January 8, 1943, and was transferred to this hospital ten days later. He had received sulfathiazole followed by a short course of sulfaguanidine, without improvement. He had been afebrile during most of the first period of hospitalization. The past history revealed an appendectomy in 1930. Personal, familial and systemic histories were noncontributory.

Physical examination on admission revealed a thin asthenic individual with evidences of recent weight loss. There was an old well healed McBurney scar. There was tenderness of the abdomen over the course of the ascending, transverse and descending colon. His temperature was 98.8° F, the pulse rate 96 and respirations 24.

A low grade remittent type of fever persisted for a period of nearly two months. The highest temperature recorded during this time was 100° F. The patient was given a soft bland diet with sedation and antispasmodic drugs. On January 21, three days after admission, sigmoidoscopic examination revealed the mucous membrane diffusely injected but no ulceration was seen. Hypertrophied lymphoid tissue was present throughout, and gross blood and mucus were in evidence. A smear taken directly from the mucosa revealed numerous red blood cells, pus cells and mucus, but no amebae or ova were found. A culture taken from the mucous membrane during this procedure showed only organisms of the B. coli group. The patient was given sulfaguanidine, the initial dose being 4 gm., followed by 1 gm. every four hours. On January 20 the white blood count was 14,300, with a differential count of 70 neutrophils, 18 lymphocytes, 1 stab cell and 11 monocytes.

On January 28 the patient was again examined with the sigmoidoscope and no essential change from the previous examination was seen. The patient showed no clinical improvement with therapy and it was discontinued on February 2. Sigmoidoscopic examination on this date revealed several punched-out hemorrhagic ulcers in the mucosa of the upper rectum. On the following day a stool examination showed gross blood, mucus, pus cells and many vegetative, motile forms of *Endamoeba histolytica*. Emetine hydrochloride 0.064 gm. (1 grain) was then administered intramuscularly once daily.

On February 5 stool examination again revealed many amebae. Abdominal pain continued and became associated with severe tenesmus. On February 6 sigmoidoscopy was again performed. The mucous membrane was edematous and grossly hemorrhagic. There was a clearly defined ulcer, oval in shape and irregular in outline, measuring about 1 cm. in diameter, in the upper rectum. Foul smelling liquid fecal material, mucopurulent and bloody in appearance, was encountered.

Emetine hydrochloride was discontinued after the ninth dose had been administered, the total dosage being 0.576 gm. (9 grains). Following this the patient developed severe abdominal pain and some tenderness over the liver area.

A flat plate of the abdomen revealed questionable hepatic enlargement. Physical examination of the abdomen was difficult because of tenderness and voluntary rigidity. Carbarsone, which had been planned as further antamebic therapy, was withheld. Stool examinations continued to show many vegetative forms of *Endamoeba histolytica*.

On February 20 the patient had a hemorrhoidectomy performed for the removal of two large, painful, thrombosed, external hemorrhoids. The postoperative course, per se, was uneventful. On March 1 a transfusion of 500 cc. of whole blood was followed by a slight reaction. No significant anemia had been present prior to transfusion but the white blood count was 26,800, with a differential count of 86 neutrophils, 13 lymphocytes and 1 monocyte. The patient seemed to be better following the transfusion but the stools continued to show vegetative forms of *Endamoeba histolytica*.

Specific therapy was again started with emetine hydrochloride on March 4, at which time the temperature was normal. The dosage was increased to 0.10 gm ( $1\frac{1}{2}$  grains) once daily intramuscularly, and chiniofon, 1 gm daily in divided doses, was given simultaneously by mouth. Treatment was continued for a full course of ten days, with considerable improvement in the condition of the patient. The blood pressure remained at a normal level throughout the emetine therapy. Examinations after the sixth day of treatment revealed no amebas or cysts, but blood and pus cells were still present. On March 18 an eight-day course of succinyl-sulfathiazole was begun. The initial dose was 15 gm, and this was followed by a dose of 2.5 gm every six hours. Steady improvement in the patient's condition continued. Sigmoidoscopy on March 26 revealed a normal bowel. The patient's weight on this date was 150 pounds. He became ambulatory and was transferred to a convalescent hospital April 15, 1943, at which time his weight had reached 164 pounds.

*Comment*—This patient represented a severe case of combined bacillary and amebic dysentery. The differential diagnosis was difficult in this case, and the laboratory findings were essential for a correct evaluation. The bacillary dysentery was not controlled until the amebic infection had been satisfactorily treated. A transfusion was given between the courses of emetine to increase the patient's resistance after a prolonged illness. Although the patient showed no signs of anemia he suffered considerable weight loss. Improvement following the second course of emetine was striking and was accompanied by the disappearance of amebae from the stools. Sulfonamide therapy was utilized following the course of emetine treatment because it was believed from the exudate in the stools and the sigmoidoscopic examinations that a combined infection was present. It was feared a chronic bacillary infection might be a sequela. The use of carbarsone was considered after the first course of emetine had proved ineffective but the idea was abandoned when symptoms and signs suggesting the possibility of an amebic hepatitis appeared.

#### DIAGNOSIS

*Laboratory Studies.*—A diagnosis of dysentery does not depend on exacting laboratory procedures, though gross and direct microscopic

examination of the feces may frequently be diagnostic. To facilitate the diagnosis, however, it is desirable to follow carefully certain established principles.

**Collection of Feces**—The entire stool is collected in a clean, dry container and should not be intermixed with urine. Stools are classified as "watery-bloody-mucus" or "ordinary," the former type being characteristic of the dysenteries. It should be examined immediately.

**Examination**—The stool is examined grossly for amount, color, consistency and odor. The presence or absence of blood or mucus is

#### THE CHARACTERISTICS OF DYSENTERY STOOLS

	<i>Bacillary</i>	<i>Amebic</i>
Gross Appearance	Early Copious watery stools with flakes of mucus. Later The stools consist of blood and mucus only. The quantity of blood varies from flecks to gross blood. Mucus is glairy white, odorless and tenacious.	Semisolid, brown fecal material foul-smelling, intermingled with mucus and blood in varying quantities. Mucus commonly a dirty brown color. The stool may consist entirely of a small amount of diffusely bloody mucus resembling "currant jelly."
Microscopic Appearance	Mucus contains masses of closely packed cells. Red blood cells present to a greater or lesser extent depending on the portion of mucus selected for study. Exclusive of red blood cells, 90 per cent of the cells are polymorphonuclear leukocytes. This acute inflammatory exudate is diagnostic of bacillary dysentery.	Polymorphonuclear leukocytes are scant. The majority of cells are red blood cells with mononuclear leukocytes and other large degenerate cells derived from the intestinal wall. Charcot-Leyden crystals are not uncommon in the mucus.
Specific Diagnosis	Isolation of <i>B. dysenteriae</i> by culture from mucoid portion of the stool.	Identification of motile amebae with presence of ingested erythrocytes is diagnostic.

noted. A loopful of mucus is placed on a glass slide, intermixed with a few drops of warm, normal saline solution and examined under a cover slip. The preparation may be kept warm by removing the mirror from the microscope and using a standard microscope lamp below the substage. If this is not available, then reflected heat from a goose neck lamp placed near the microscope is adequate. The preparation may be examined under the low power objective for amebae, but it may be more satisfactory to utilize the high power objective with a 6X eyepiece for stool examinations. The exudate is examined for motile amebae, erythrocytes and leukocytes especially noting the relative proportion of polymorphonuclear leukocytes in the preparation. The presence of Charcot-Leyden crystals is of significance in

amebic dysentery Essential diagnostic criteria are outlined in the accompanying table

**Specific Diagnostic Criteria—1 *Bacillary Dysentery***—Bacteriologic cultures and isolation of a specific organism from the stool are necessary if a positive diagnosis of bacillary dysentery is to be made. Experience has taught us that a larger percentage of positive cultures will be obtained if a sterile gloved finger or swab is inserted into the rectum and the mucus obtained placed in 5 cc of sterile normal saline solution of peptone water. A loopful of this is placed on selective media (For specific bacteriologic technic, refer to standard laboratory textbooks)

**2 *Amebic Dysentery***—An absolutely fresh stool is collected and a loopful of the mucoid exudate is selected for study. The *Endamoeba histolytica* is readily found under high power magnification, but should be closely examined for detail under the oil-immersion lens. It is a refractile, single cell organism about two or three times larger than a polymorphonuclear leukocyte. The amebae are actively motile, and their movement is characterized by the extension of a pseudopod toward which it flows. The presence of ingested red blood cells in the motile organism is diagnostic. As the specimen grows cold, motility ceases. Warming of the glass slide will enhance motility and inactive amebae may become motile.

*Endamoeba histolytica* must be differentiated from *E. coli*, which is nonpathogenic. The latter does not ingest red blood cells. A common error is to confuse macrophages (monocytes with ingested cellular debris, pyknotic red blood cells or fat globules) with dead amebae or amebic cysts. It should be emphasized that amebic cysts are usually not associated with acute dysentery but are found in well formed stools. The internal structure of cysts characterized by 1 to 4 nuclei and rhomboidal bars (when the specimen is stained with a few drops of 1 per cent solution of iodine and potassium iodide) is readily seen.

**Sigmoidoscopic Findings**—In *bacillary dysentery* the typical sigmoidoscopic picture presented was that of a diffuse inflammation of the bowel mucosa. The mucosa was edematous and friable, and numerous punctate hemorrhages were found throughout. A sanguineous mucoid exudate was often present in the bowel lumen. The pathological process involved the anal crypts, rectum and distal sigmoid as far as could be visualized. In some cases the small punctate hemorrhages were found to have broken down forming pinpoint ulcers which involved only the mucosa. As the patient recovered, the sigmoidoscopic picture changed. The edema of the bowel mucosa was the first to disappear, then the areas of hemorrhages became darker in color and the bowel returned to normal rapidly after the subsidence of symptoms.

The sigmoidoscopic picture in a typical case of *amebic dysentery* presented an entirely different picture. The bowel mucosa was normal except for areas of ulceration. The ulcers present were small and

irregular and frequently extended through the mucosa and were undermined. There was no mucosal inflammation except in the cases with mixed infections (bacillary and amebic, of which several were seen). In these cases the bowel mucosa appeared more like that seen in the bacillary group. Ulcers, when present, were difficult to visualize. Little difficulty was encountered in performing sigmoidoscopic examinations, except in the more severely ill patients with tenesmus and very frequent stools. Best results were obtained by examining the patients early in the morning before any food was taken and without any special preparation for the procedure.

#### DIFFERENTIAL DIAGNOSIS

One of the first problems which confronted us in the differential diagnosis of the dysenteries was the confusion which existed in the minds of local authorities. They considered that all cases of dysentery on the island were amebic in origin. They made a specific diagnosis on the presence of macrophages which they called "dead amebae." However, the acute onset, the toxic condition of the patient, and the frequent stools which were first liquid in character were not characteristic of amebic dysentery. Furthermore, the characteristics of the stool and the sigmoidoscopic examinations ruled out *Endamoeba histolytica* as the cause of the current epidemic. Although at this time our hospital was not equipped for complete bacteriologic studies, other Army hospitals were able to isolate the Sonne strain of *Shigella dysenteriae* in similar cases.

The disease, prior to the onset of diarrhea, often simulated *acute appendicitis*. In those patients with abdominal pain, vomiting, low grade fever, leukocytosis and abdominal tenderness—at times most marked in the right, lower quadrant—the differentiation was at times most difficult. This was especially true in those in whom the appearance of diarrhea was delayed. In a few instances, patients with these findings were operated on. The appendix was normal. Typical bacillary stools occurred after the operation. Following this, careful observation of such patients obviated unnecessary operations.

"*Acclimatization diarrhea*," a symptom complex described by medical officers of the New Zealand Armed Forces in the Middle East, frequently had to be considered. This syndrome is found in unseasoned troops in hot climates and is characterized by severe cramps and diarrhea. Usually this is the result of dehydration and salt imbalance. The nonspecific character of the stool and the minimal symptoms which clear rapidly after hydration has been established differentiates this syndrome from bacillary dysentery.

#### COMPLICATIONS

There were few complications in the patients treated. A low grade nonspecific proctitis and cryptitis followed some of the more severe



cases of the bacillary type. This responded slowly to symptomatic and local therapy. The most difficult therapeutic problems were those cases with combined amebic and bacillary dysentery or with amebic dysentery complicated by secondary infections. In one of these patients (Case III) an amebic hepatitis was suspected, and a hemorrhoidectomy was necessary for acute thrombosed external hemorrhoids.

#### PREVENTION

Isolation of all dysentery patients is essential. Whenever possible they should be kept in a screened ward, but in the field this is seldom possible at the time when most cases are being seen. However, some method must be improvised to prevent secondary cases. Screened kitchens and mess halls will usually not become available until the hospital has been established for some time. It is thus the responsibility of the ward officer to prevent the spread of the disease among the hospital personnel and other patients. It was our custom to build a wooden frame at the end of the tent ward large enough to accommodate two bucket commodes. This frame was provided with a door and the whole covered with salvaged mosquito netting. Ambulatory patients used this fly-proof latrine. Bed patients were given individual bed pans whenever possible. These were carbolyzed and kept under mosquito bars, out of doors.

A daily inspection of the mess halls and kitchens should be made. Food must be covered and lids firmly placed on garbage cans. The cans must be emptied several times a day into a screened garbage seepage pit or an incinerator. Fly paper and insecticide sprays may be utilized. All natives should be kept away from the kitchens and special care must be taken to see that natives do not defecate near the hospital area.

The water supply must be filtered as well as chlorinated. Amebic cysts are not destroyed by the chlorination of water in the strength of one part per million. It is surprising how many medical officers fail to appreciate this. The establishments of water points employing the standard U. S. Army Engineer filtration and chlorination apparatus, and using water drawn only from these points, is a simple measure which eliminates this source of infection.

It is also necessary to restrict the use of fresh uncooked vegetables and fruits purchased from natives. It is wise to avoid uncooked vegetables entirely. The soldier must be educated to the dangers of eating in native establishments where sanitary precautions are lax or nonexistent.

#### TREATMENT

Symptomatic therapy is of value in all types of dysentery. Relief of cramps and abdominal pain may be obtained in the milder cases by phenobarbital and codeine in doses of 0.032 gm ( $\frac{1}{2}$  grain) each, every four hours. Tincture of belladonna in doses of 1 cc or atropine sul-

fate 0.0006 gm. (1/100 grain) may be used with the above drugs. Morphine sulfate in full doses hypodermically may be necessary in severe cases. Application of heat to the abdomen may be comforting. The diet should be liquid or soft bland, and fruit juices and coffee should be avoided. Cream soups, toast, soft cooked eggs, cooked cereals, gelatin and custards are usually well tolerated. Intravenous solutions of glucose in physiological saline should be given when dehydration is evident or vomiting present.

**Bacillary Dysentery**—In mild cases of bacillary dysentery similar to the first case described it was found that patients responded nearly as rapidly to symptomatic therapy alone as to sulfonamide therapy. Those patients who presented a relatively high fever with general symptoms and severe bowel manifestations were usually treated with *sulfaguanidine*. At first, the drug was employed in an initial dose of 4 gm. followed by 1 gm. every four hours. Later the plan of treatment was changed to an initial dose of 7.5 gm. with 3 gm. every four hours until the stools were reduced to three or four per day. Beneficial results were obtained rapidly as a rule. It was found desirable to continue the *sulfaguanidine* in doses of 2 or 3 gm. four times per day for at least two days after the bowel movements had become normal. This seemed to aid in preventing relapses.

A few cases were treated with *succinylsulfathiazole* (sulfasuxidine), which was available to us in limited amounts. The initial dose of this drug was 15 gm., and this was followed by a similar dose in divided amounts given in each subsequent twenty-four-hour period. The drug was found to be as effective as *sulfaguanidine* in the few cases in which it was employed.

Other sulfonamides, such as *sulfathiazole* and *sulfadiazine*, have been found effective in bacillary dysentery, although they are probably less efficacious than *sulfaguanidine*. Sodium bicarbonate should be given with these sulfonamides in doses of approximately twice that of the sulfonamide, and fluids forced. With *sulfaguanidine* and *succinylsulfathiazole* bicarbonate is not necessary. Toxic effects from the latter drugs are infrequent because of their insolubility, but have been reported. The soluble sulfonamides are employed in the usual dosage for these drugs, which is considerably less than that for *sulfaguanidine*.

Recently some success has been reported in the chemical prophylaxis of bacillary dysentery by the use of sulfonamide drugs. Spread of epidemics has apparently been arrested by giving sulfonamides to those exposed to the infection. Further observations are necessary to determine the value of this type of therapy but if successful it offers an important means of controlling this disease in troops and in institutions.

**Amebic Dysentery**—Good results were obtained in the treatment of amebic dysentery with *emetine hydrochloride* given once daily intramuscularly. The usual dose employed was 0.064 gm. (1 grain) daily.

for eight to ten doses. In a few patients larger doses (0.1 gm [1½ grains]) were found advisable. *Chiniofon*, in divided doses of 1 gm. daily by mouth, was given coincident with emetine. No toxic effects from emetine were encountered, though the patients were examined daily including blood pressure recordings. Muscular soreness at the site of injection was nearly universal. This disappeared within a week after completing the treatment.

Combined treatment with *emetine hydrochloride* and *carbarsone* has been advocated as less toxic and possibly more effective for the average case of amebiasis. The emetine is given as above for four to six doses, and carbarsone, 0.25 gm (4 grains), is given three or four times daily for seven days, either concurrently or following the emetine.

### SUMMARY AND CONCLUSIONS

1 The prevention of endemic and epidemic dysentery among troops is of great importance in the successful prosecution of the war.

2 The common fly is the main vector in the transmission of bacillary dysentery. Contaminated food was the chief source of amebic dysentery in our cases.

3 The essential diagnostic criteria of bacillary and protozoal (amebic) dysentery are presented.

4 A difficult condition to diagnose and treat is combined bacillary-amebic dysentery or amebic dysentery complicated by secondary infection.

5 The enforcement of sanitary measures regarding latrines, kitchens and mess halls is fundamental in preventing epidemics of bacillary dysentery. Chlorination and filtration of all water supplied to troops, and the cooking of all vegetables and fruits when from native sources, will minimize the danger of amebic dysentery.

6 Specific chemotherapy is now available for both types of dysentery. The results with the use of sulfonamide drugs in the treatment of severe bacillary dysentery are especially encouraging.

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# ANXIETY NEUROSIS MANIFESTED BY CARDIOVASCULAR SYMPTOMS (NEUROCIRCULATORY ASTHENIA)

LT COLONEL JOSEPH B VANDER VEER

MEDICAL CORPS, ARMY OF THE UNITED STATES

THE institution of selective service prior to our entrance into the present war stimulated renewed interest in the syndrome which has in the past been termed neurocirculatory asthenia. The condition is of relatively minor importance in civil life and little had been done to elucidate the problem since the work of Sir Thomas Lewis during and just after World War I. First described by Stillé and by Hartshorne in 1863, the best early résumé of the syndrome was by DaCosta<sup>1</sup> in 1864. Tachycardia, dyspnea on exertion, debility and fatigue were recognized as salient features of the condition. No cardiac abnormalities except tachycardia were found on physical examination. It was thought to be due in some way to army life and it was found that hospital care "improved" but did not necessarily cure the patient. In one year, during World War I, the British Military Heart Hospital treated 558 patients with this syndrome. Four-fifths of these soldiers were from the battlefields of France.<sup>2</sup> It is of interest, however, that in a general hospital in the United States there were 300 patients of this type in one year and practically none of these had been in the combat zone.

To date in World War II the problem of "neurocirculatory asthenia" in soldiers on overseas duty seems to be of less importance than in the previous war. Whether this is due to a better screening of the men inducted, to better physical and/or mental health of the troops or to a somewhat different viewpoint on the syndrome, remains to be determined.

## ANALYSIS OF TEN CASES OF NEUROCIRCULATORY ASTHENIA IN SOLDIERS OVERSEAS

For a period of over a year it was our privilege to function as a fixed hospital for the troops on an island in the South Pacific area. In this time a number of patients with neurocirculatory manifestations of a functional type were studied. Most of these patients had been in the Army for about one year before going on overseas duty and were considered in good physical condition. They were not under combat conditions or undergoing undue hardships. The patients studied had a variety of complaints and numerous tentative diagnoses had been made prior to hospital admission.

**Symptoms.**—Because of the varied symptomatology and manifestations of this syndrome it is perhaps of more value to consider a num-

ber of these patients as a group rather than as individual case reports. An analysis of the symptoms and findings in ten representative patients with neurocirculatory manifestations sufficient to cause hospitalization was made. The patients varied in age from twenty-three to thirty-three years, the average age being 27.5 years. The most common complaints were *shortness of breath on slight or moderate exertion* and *easy fatigue*. These were both present in nine of the ten patients. All but two of the patients had "*weak spells*" which varied in intensity and duration. They were usually related to the upright position, and *mild vertigo* was common. Two gave a history of definite syncopal attacks.

*Heart "consciousness" and palpitation on exertion* were present in six cases. *Precordial pain* was a frequent symptom, being present in five of the ten patients. In one it was sharp in nature and transient but in the remainder it was described as a dull ache or tightness over the cardiac region. In none was it primarily substernal. There was no significant radiation of the pain. It was apt to occur either with exertion or at rest. When precordial distress was precipitated by exertion, there was no tendency for it to become increasingly severe as the exertion continued. It frequently was noted at rest some time after exertion (i. e., following a march). In one other patient there was a sharp but nonpleuritic pain in the right chest.

Three patients gave a history of "*shortness of breath*" at rest. When they were questioned as to the nature of this difficulty it was found to consist of the typical sighing respiration characteristic of the neuroses and variously described as "not being able to get a deep breath," "the air not going deep enough" or "not a satisfactory amount of air." One of these patients had no shortness of breath on exertion and the others said the dyspnea of effort which they experienced was different from the distress noted at rest. Tremor of the hands was a complaint in three patients and in two frequent headaches were present. The nature of both suggested they were of neurogenic origin. It is of interest and importance that half of the patients had experienced similar symptoms during one or more periods in civil life.

**Physical Examination**—Physical examination revealed that manifestations of nervous system imbalance were common. *Cold moist hands*, frequently with a coarse tremor and increased tendon reflexes, were nearly always the rule. *Increase in the pulse rate at rest*, especially in the upright position, was common. With the patient in the supine position four of the ten patients had a heart rate per minute of 84 or below, in four the rate was between 85 and 100 and in two it was above 100. With the patients standing, only one had a rate below 84, five had a rate between 85 and 100 and in four the rate was persistently above 100. The *blood pressure* tended to be labile but was considered to be within limits of normal in one half of the patients. In five there was a tendency for slight elevation, especially of the systolic pressure.

The readings (average of several) for these five patients were 150/90, 140/88, 150/76, 144/90 and 150/90. In none was the blood pressure found at a low level, the lowest recorded pressure being 120/64.

There was no evidence of organic cardiac disease in any of the ten patients. In two, rather loud *systolic murmurs* were present in the area of the pulmonic cartilage. These varied in intensity with position and different respiratory phases and were definitely "functional" in type. Occasional *premature contractions* were present in two patients. The finding of *increased activity over the precordium* at inspection and palpation was common, especially at the beginning of the examination. This seemed due in most cases to a combination of an active heart and a thin chest wall, a condition analogous to that frequently seen in hyperthyroidism with which the neurocirculatory syndrome may occasionally be confused. Three of the patients had been told at some time previously that they had "heart trouble." Two of these three and one other patient had been rejected for military service one or more times before final acceptance, apparently because of findings related to the cardiovascular system.

**Laboratory Studies.**—In none of the patients did the laboratory studies reveal any significant abnormalities. Urinalyses were normal and there was no anemia. Fluoroscopic examination frequently revealed overactive pulsations of the heart but there were no abnormalities of contour in the anteroposterior or oblique positions. None of the patients showed cardiac enlargement as measured on a 6-foot film and calculated according to the tables of Ungerleider and Clark.<sup>3</sup>

**Exercise Tolerance Test.**—A simple exercise tolerance test was done routinely as a measurement of the individual's response to moderate exertion. The resting pulse was recorded with the patient standing. The patient then hopped twenty times on each foot raising the toe 4 to 6 inches from the floor. The pulse was taken immediately after exercise and after one and two minutes. The response of the average normal soldier was a rise in the pulse rate of 20 to 40 beats per minute following exercise, a return nearly to the pre-exercise level in one minute and to the original level or slightly below in two minutes. In patients with "neurocirculatory asthenia" the common response was an unusually high pulse rate after exercise and a failure to return to the pre-exercise level within two minutes. In some patients with rather marked tachycardia before exercise, further increase in the pulse rate after exercise was not marked, but failure to return to the pre-exercise rate after two minutes was still present. More than one observation of this test was necessary to eliminate psychogenic and other factors. In patients recovering from severe illnesses the response to exercise tests may be similar to that seen in neurocirculatory asthenia. Such tests may be used as a measurement of improvement in the patient's cardiac reserve and general condition. The accompanying table illustrates the response to this test by different individuals. In two of

the ten patients with neurocirculatory asthenia the response to the exercise test was essentially normal. In four it was definitely abnormal and in four markedly abnormal.

PULSE RATES TYPICAL RESPONSES TO AN EXERCISE TOLERANCE TEST

	Normal Soldier, Over- weight	Normal Soldier, Average Build	Case No. 2, "Neuro- circulatory Asthenia"	Case No. 8, "Neuro- circulatory Asthenia"	Patient Recovering From Severe Illness	
					Just Ambula- tory	Six Weeks Later
Sitting			104	108	104	68
Standing	68	80	132	128	120	92
Immediately after 40 hops	116	100	152	156	172	140
One minute after hop	80	68	144	142	140	100
After 2 minutes	60	64	140	148	140	84

## COMMENT

**Etiology**—The neurocirculatory syndrome is now largely regarded as a manifestation of an anxiety neurosis rather than a specific disease process. The condition is more apt to develop in certain types of individuals. Constitutionally inferior persons, chronic invalids, emotionally unstable persons and those of asthenic habitus are the most prone to develop the syndrome. Lewis<sup>2</sup> recognized that the psychology of the patients as a group was not that of the average soldier. In a large proportion of his cases the patients were of a highly strung, nervous temperament, many were sensitive, querulous or depressed and an unusually large proportion eschewed the use of alcohol for conscientious reasons.

An excellent view as to the common causative factors in the production of war neuroses is given in a discussion of the subject in a recent publication.<sup>4</sup> "How to be brave and safe—that is the greatest psychological problem for the soldier. Most of the war neuroses (mental illness) result from the failure of men to find any sort of satisfactory way out of that dilemma. If a man goes on being torn by his conflicting desires—if he cannot bring himself to go forward, yet is too conscientious to give up—he will suffer from the type of neurosis characterized by anxiety. He finds he can no longer concentrate. He becomes confused. The expression on his face, his pulse rate, his rapid breathing betray the fierce battle going on within him. He himself may not be fully aware of the cause of the terrible sense of fear and horror that seems to hang over him. Yet he is, in a way, solving his problem. He is making himself too inefficient to continue

in the fight, yet giving himself so much suffering that his conscience cannot accuse him of taking the easy way out. Yet, even so, he does not know that he is doing all this. His nervous system does it for him."

Other precipitating, emotional factors in soldiers are concern for the safety and financial security of dependents, loss of affection of wife or sweetheart during separation, resentment of authority and an aversion to regimentation.

There are other conditions which may be predisposing or contributing factors in a susceptible individual. Infectious diseases, fatigue and emotional trauma frequently precede the onset of the syndrome. However, the personal element seemed to be the most important etiologic factor in our patients. In none had the symptoms followed combat duty or extremely difficult living conditions. Previous infections did not play a significant role. In two patients, major psychiatric episodes were certainly contributing factors. Had thorough psychiatric study of these patients been available it seems likely that more disturbances of this type would have been discovered. The onset of symptoms is apt to be coincident with added responsibilities. In the army this is often seen in newly commissioned officers who have risen from the ranks.

**Diagnosis.**—The recognition that functional diseases have as definite a positive history as have organic conditions is essential in the proper understanding and diagnosis of this syndrome. The nature of the symptoms and their occurrence under conditions which would not produce such distress in a normal individual should at once arouse the suspicions of the physician. Evidence of circulatory imbalance are usually present. Slight tachycardia at rest, with an unusual increase in heart rate on standing is suggestive. A labile blood pressure is common, and cold moist hands and feet are nearly the rule. When precordial pain is present the location and character suggest a nonorganic etiology. "Sighing" respirations are common as in other neuroses and may pass under the guise of "shortness of breath" if a careful history is not obtained.

Laboratory examinations rarely yield additional information. Negative x ray and electrocardiographic studies may be of aid in reassuring the patient that serious disease is not present, they seldom show any abnormalities. Complete blood count and urinalysis are of course desirable. Anemia, hyperthyroidism, latent infections and tuberculosis are conditions which must be considered in differential diagnosis. Prolonged hospitalization with multiple laboratory examinations only serve to make the patient suspect that the doctor is unable to locate the trouble. This is true in both military hospitals and civil practice. The best interests of the patient are usually served by a rapid, thorough work-up including only the definitely indicated laboratory studies.

**Prognosis.**—The prognosis of an anxiety neurosis depends a good



deal on the circumstances surrounding its development. In patients who have had similar difficulties in civil life and in those in whom it develops without undue stress and strain the outlook for a satisfactory recovery is not good. In those in whom the symptoms develop for the first time after severe combat conditions with exhaustion, weight loss and lack of sleep, the prognosis may be fairly good if the patient can obtain the proper care. The same holds true of patients developing the syndrome following acute infections or severe illnesses. The basic background of the individual is of course important, and in those who are constitutionally inferior and unstable, satisfactory recovery is unlikely. In general, then, the more severe the external conditions under which the syndrome develops, the better the prognosis, provided proper care is available.

**Treatment**—*Prophylaxis* is of great importance in the therapy of this syndrome. Individuals who have a clear-cut history of neurocirculatory disturbances should be rejected for military service. The many cases already in the Army and those which will develop under combat and precombat conditions present an important problem. Early recognition of the condition may lead to the salvage of many of these individuals. Prolonged hospitalization with transfer from one hospital to another is very apt to lead to invalidism. The quicker the proper therapy is instituted the more likely is the patient to make a satisfactory recovery.

There are no drugs of value in the treatment of neurocirculatory asthenia and bed rest may be detrimental. Prolonged investigation without attempt at therapy or alleviation of the patient's symptoms causes him to lose faith in his physician. Organic disease should be quickly excluded in the diagnosis, and usually a thorough history and physical examination will do this. The natural course of many of the patients is toward recovery. Measures to improve the general health are indicated. Secondary anemia, malnutrition, foci of infection and any other secondary factors should be corrected.

The nature of the condition should be explained to the patient and every effort should be made to gain his confidence. He should understand why the symptoms occur and that they are not the result of serious disease. Assurance must be given that the symptoms even if persistent will not lead to cardiac or other disease or cause invalidism later. Re-education is an important item. The patient should be kept occupied mentally and given tasks to do which involve some physical exertion and responsibility even though some symptoms are produced. He is apt to do too little rather than too much. Whenever possible the patient's work and everyday life should be adjusted to avoid the stresses and strains that upset him and produce symptoms. This may be difficult even in civil life and is apt to be more so in the military service. However, with a proper understanding of the condition by the physician and patient, some place can usually be found where the

soldier or civilian may do a useful job. Manpower is thus saved at an important time and the self-respect of the individual is preserved.

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# FRACTIONAL GASTRIC ANALYSIS A SIMPLIFIED TECHNIC WITH INTERPRETATION OF RESULTS

CAPTAIN ALEXANDER RUSH

MEDICAL CORPS, ARMY OF THE UNITED STATES

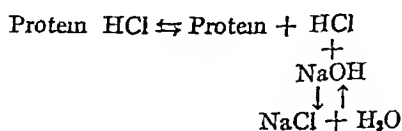
Just how important is gastric analysis and of what practical value is it in the differential diagnosis of gastro-intestinal disorders? Are the results worth the time and the labor involved? No one can tell how often these and similar questions concerning the significance of the findings of a gastric analysis have arisen in the minds of hard-pressed medical and laboratory officers operating under the handicaps of war-time conditions. Nevertheless, in many hospitals, fractional gastric analysis as a routine measure in the study of patients with digestive complaints continues to be carried out in accordance with time-honored custom. It is the purpose of this paper to review briefly the principles and interpretation of gastric analysis in the light of recent studies and to add a few observations made in a field hospital overseas.

Gastric analysis as a measure of the secretory capacity of the stomach has long maintained an established position in the differential diagnosis of diseases of the digestive system. With the passage of time, many different methods of performing the test have been introduced. Each, however, is based upon one of two physiological reactions: (1) the secretory response to the ingestion of a test meal, (2) the response to the injection of a chemical stimulant. While various test meals are still widely employed, the present trend is toward carrying out a fractional gastric analysis following the injection of a standard chemical stimulus.

## PHYSIOLOGIC BASIS OF GASTRIC ANALYSIS

Since the discovery that gastric juice contains hydrochloric acid, evidence has accumulated in support of the following conclusions regarding the nature of this secretion. The hydrochloric acid of gastric juice is derived from the parietal cells of the gastric mucosa. This acid behaves like chemically pure hydrochloric acid of similar strength.<sup>1</sup> A small portion of the hydrochloric acid is loosely combined with protein-like substances in the gastric contents and splits off in the presence of excess alkali in accordance with the law of mass action.

Thus



In the presence of increasing amounts of "free" hydrochloric acid, a condition which exists following successful stimulation of acid secretion, the reaction depicted above proceeds to the left until the maximum combination of protein with acid has been attained. All hydrochloric acid in excess of that "combined" with protein remains "free" and behaves as a pure mineral acid. In the presence of increasing amounts of alkali, a condition which obtains during titration of acid juice with sodium hydroxide, the "free" hydrochloric acid is first neutralized and the reaction proceeds to the right. When a hydrogen ion concentration of 4.0 is reached (change of color from red to yellow with Topfer's reagent) the neutralization of the free hydrochloric acid is complete. When the titration is carried to pH 9.0-10.0 (end-point of phenolphthalein), neutralization of the "total" acidity, i.e., free hydrochloric acid, combined hydrochloric acid acid salts and organic acids is complete.<sup>2</sup> The physiologic and clinical significance of these titrations is important. Pepsin, the protein digesting enzyme, becomes inactive at hydrogen ion concentrations greater than 4.0.<sup>1</sup> Since there is reason to believe that peptic ulceration of the mucosa takes place *only* in the presence of "free" activating hydrochloric acid,<sup>3</sup> it is the aim of the alkali treatment of peptic ulcer to maintain the gastric contents at a concentration greater than 4.0. In some forms of macrocytic anemia in subacute combined degeneration of the spinal cord and diffuse atrophic gastritis there is reason to believe that a severe atrophy of the secreting cells of the gastric mucosa has taken place.<sup>4</sup> As part of the clinical findings of these diseases there is almost invariably complete achlorhydria, i.e., no free hydrochloric acid is released in response to an adequate stimulus, such as histamine.

Pavlov believed that the hydrochloric acid of gastric juice was secreted at a constant, high concentration.<sup>5</sup> The concentration of acid at any given moment was considered proportional to the intensity of the stimulus. More recent studies,<sup>6</sup> while supporting the concept of the secretion of an acid of constant, high concentration have modified somewhat the interpretation of the varying levels of hydrochloric acid. To be specific, the concentration of free hydrochloric acid of any sample of gastric juice represents a balance between the forces tending to raise the concentration of acid and the forces tending to lower it. The liberation of hydrochloric acid is influenced by a number of factors. On the one hand, there is the physiological condition of the parietal cells, on the other the character of the stimulus. Stimuli to gastric secretion may be pharmacological or physiological. Following parenteral injection, the former stimuli act upon the secreting mechanism in accordance with their pharmacological properties. The physiological stimuli may be considered in terms of the three familiar phases of gastric secretions: (1) the psychic phase, in which the stimulus to secretion is mediated by way of nervous pathways in response to the sight, taste, or smell of palatable food, (2) the gastric phase, in which

the stimulus is in the form of an internal secretion of hormone (gastrin) which is liberated by the action of certain food substances upon the mucosa and is carried by way of the blood stream to the reacting cells,<sup>7</sup> (3) the intestinal phase, in which the stimulus is the product of the interaction of certain food substances and the secretions of the intestinal mucosa, which, on being absorbed into the general circulation, act on the gastric secretory mechanism

Those factors which tend to reduce the acid concentration of the gastric contents and offset the effects of stimulation can be described as (1) psychic, (2) hormonal, (3) chemical, (4) reflex, (5) anatomic. The sight or taste of palatable food under disgusting or revolting surroundings ordinarily fails to promote gastric secretion.<sup>8</sup> The disagreeable sensations aroused by unpleasant conditions have an inhibitory effect upon the secreting mechanisms.<sup>9</sup>

The *hormonal* counterbalance is a product (enterogastrone) of the action of certain substances, notably fat, upon the mucosa of the duodenum and is carried by way of the blood stream to the gastric mucosa where it exerts a prolonged inhibitory influence on the secretion of acid.<sup>10</sup>

*Reflex* inhibition (enterogastric reflex) occurs when the duodenal cap is distended, the stimulus being mediated through nervous pathways.

The *chemical* factor has three aspects. First, there is the diluting effect of various secretions such as gastric mucus, swallowed saliva and regurgitated intestinal contents as well as ingested materials. Second, is the neutralizing and buffering effect of these same substances. Third, is the inhibitory effect of excess free hydrochloric acid.

The final factors that play a part in the reduction of acid are *anatomical* or *physical*. Rapid evacuation of acid gastric contents naturally would tend to reduce the amount of acid to be neutralized in the stomach. Perhaps of greater importance is the element of diffusion. Bengt Ihre<sup>11</sup> and his colleagues have demonstrated that there may be a rapid exchange across the gastric membrane of the hydrogen ions of the hydrochloric acid of gastric juice with the sodium ions of the blood. In fact, there appears to be a reciprocal relationship in the diffusion of these two ions. Since under the conditions of their experiment there was no appreciable change in volume of the gastric contents, the process seems to be one of simple diffusion.

#### RESULTS OF INVESTIGATION

Our findings are based upon the results of routine studies made upon a group of 200 patients admitted to a large army hospital in the South Pacific because of digestive complaints. Our discussion will be limited largely to the findings in patients with functional disturbances of the large bowel and in patients with diagnosed peptic ulcer. It would have been advantageous to include observations on a com-

parable group of normal subjects, but because of the limited laboratory facilities, only a small number of healthy soldiers could be studied. On the other hand, it is felt that a comparison of the results of gastric analysis in two common conditions which are frequently difficult to differentiate is instructive and serves a useful purpose.

In America, the subcutaneous injection of histamine acid phosphate or hydrochloride is widely considered the most effective standard stimulus to gastric secretion. It is believed to exert its effect directly upon the acid secreting cells and is unaffected in most instances by psychic inhibitory factors. Unfortunately, no histamine was available

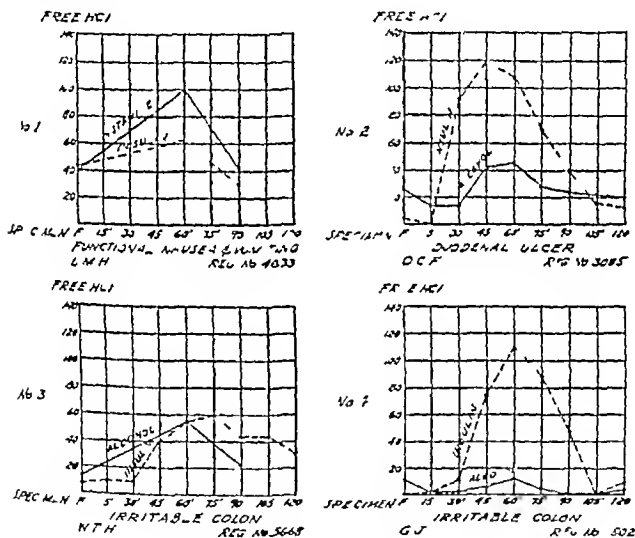


Fig 131--Titration curves in clinical units.

to us until very late in the investigation. As a substitute insulin was injected intravenously in doses of 1 unit of regular insulin per 10 kilograms of body weight. In contrast to the action of histamine, the intravenous injection of insulin brings about increased acid secretion through the effect of lowered blood sugar upon the vagal centers. No unpleasant side reactions were encountered. The secretory response to insulin seemed to be as satisfactory as that to histamine although few comparisons were made in the same patient (Fig 131, No 1). Upon emptying the stomach at regular intervals of fifteen minutes, it was found that the secretory response in most instances made it

first appearance in specimens taken thirty minutes following the injection and was complete in 120 minutes (Fig 132)

In a small number of patients, 200 cc of 7 per cent alcohol was administered as a test meal. The maximum acid values obtained in response to alcohol stimulation paralleled the distribution of those obtained in response to insulin but differed in that the highest con-

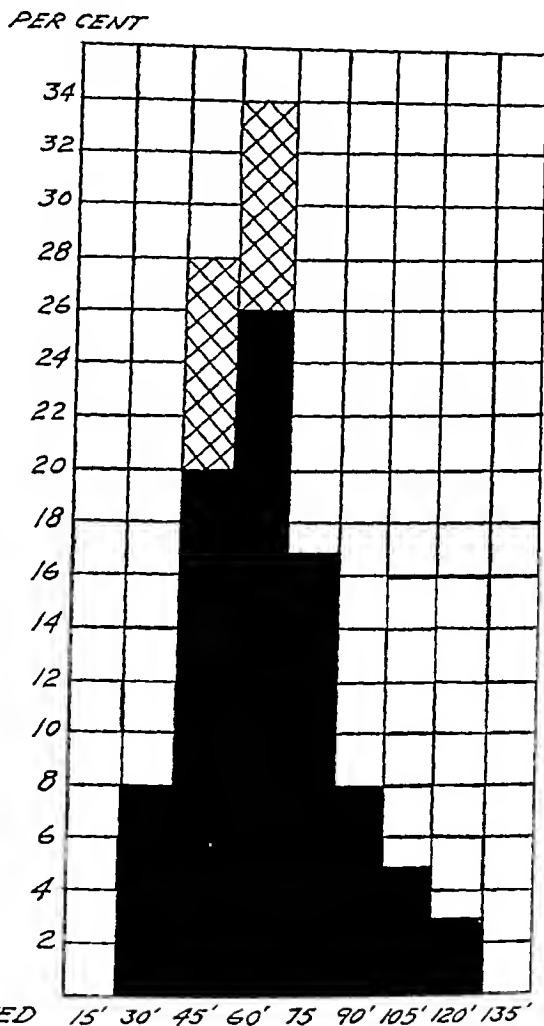


Fig 132 —The frequency in per cent of total tests (64) with which the maximum free hydrochloric acid response occurred during each period of collection of gastric contents following the intravenous injection of insulin

centration in any individual sample was less than 80 clinical units, which was the mean concentration for insulin stimulated juice. It was characteristic, too, of the response to alcohol that the acid values in addition to being generally lower were more variable and followed a less definite pattern (Fig 131, Nos 2, 3 and 4). With one exception, the same patients who failed to secrete hydrochloric acid in response

to alcohol did not respond to insulin. No data are available regarding the response of these subjects to histamine

When the results of insulin stimulated secretion in patients with peptic ulcer and irritable colon were compared, it was found that the range of the acid values extended from 13 to 128 clinical units and was the same for the two conditions. There was a slight difference in the distribution, in that in peptic ulcer there were a few more observations above the mean. In irritable colon the situation was reversed. In normal subjects the values were distributed equally on either side of the mean (80 clinical units). These differences do not appear to be sufficiently great to warrant drawing any conclusions. At most they indicate a trend. An attempt was made to correlate the volumes

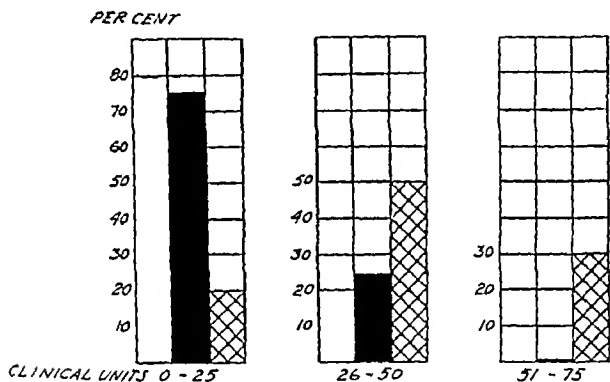


Fig. 133—The percentage of patients with diagnosed irritable colon (black) and peptic ulcer (hatched) whose free hydrochloric acid concentration of fasting juice fell within the indicated ranges as compared with subjects free of digestive disorders (white)

of gastric juice obtained in response to stimulation with insulin. While the findings roughly parallel the acid levels, there were greater variations in the curves.

In addition to our studies on stimulated secretion, the fasting juice was examined with regard to volume and acidity. This investigation was prompted by recalling the observations of Winkelstein that in duodenal ulcer there is often a continuous high night secretion. In contrast to the lack of marked difference in stimulated secretion, it was found that in irritable colon 75 per cent of the fasting specimens exhibited a free acid concentration between 0 and 25 clinical units as compared to 20 per cent in peptic ulcer (Fig. 133). In the next higher range similar differences were noted. In irritable colon 24 per cent



fell between 25 and 50 clinical units as compared to 50 per cent in ulcer. There was only one instance in which the specimens from patients with irritable colon revealed an acidity higher than 50 clinical units. This is in sharp contrast to the finding of 30 per cent above this level in peptic ulcer.

A comparison of the fasting volume and acid levels of peptic ulcer patients with those of all patients admitted because of gastro-intestinal complaints is of interest (Fig 134). Based upon the relative frequency

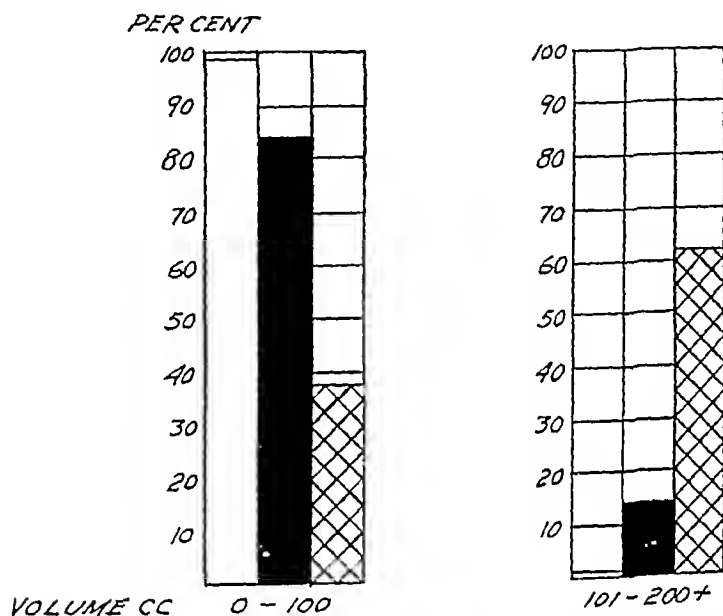


Fig 134.—The percentage of patients with diagnosed irritable colon (black) and peptic ulcer (hatched) whose total volume of fasting gastric juice fell within the indicated ranges as compared with subjects free of digestive disorders (white)

of the observations within each range, it is possible to construct rough odds as to the possibility of any single value being associated with peptic ulcer.

Range	Odds
(1) Free HCl fasting contents	
0-25 clinical units	10-1 against ulcer
26-50 " "	5-4 against ulcer
50-75 " "	4-1 in favor of ulcer
(2) Volume fasting contents	
0-100 cc	6-1 against ulcer
100-120 cc	7-3 against ulcer
120- cc	3-1 in favor of ulcer

The distribution of acid concentrations in irritable colon presented no appreciable deviation from the findings in normal subjects.

When the volume of the early morning fasting secretion was studied it was observed that only one normal subject in eleven had a fasting content greater than 100 cc. In 83 per cent of cases diagnosed as irritable colon, fasting volumes less than 100 cc. were obtained while in the remaining 15 per cent the volumes ranged between 100 and 120 cc. In no instance was a volume above 120 cc. obtained. These figures differ significantly from those obtained in peptic ulcer patients. In the latter disease only 38 per cent of the patients had fasting volumes of less than 100 cc., while 13 per cent had volumes between 100 and 120 cc., and 49 per cent or almost half the ulcer patients yielded fasting volumes greater than 120 cc. These figures suggest that a fasting volume greater than 100 cc. is probably abnormal, while any volume greater than 120 cc. is likely to be associated with the ulcer diathesis or an obstructive lesion at the pylorus. However, it should be pointed out that a fasting volume of less than 120 cc. does not exclude ulcer.

As a result of these observations, an attempt has been made to simplify as much as possible the procedure of gastric analysis. This endeavor was further prompted by the fact that the laboratory facilities for titrating a large number of fractional specimens were limited. The technic which was finally adopted follows:

#### ABBREVIATED PROCEDURE FOR FRACTIONAL GASTRIC ANALYSIS

- 1 Nothing by mouth after midnight preceding test
- 2 Pass Levin or Rehfuess tube and completely empty stomach by aspiration. Collect in a container and label "Fasting Specimen."
- 3 To fasting specimen add 2 or 3 drops of alcoholic solution of dimethylamino azobenzene (Topfer's reagent)
- 4 If the sample develops a red color, discontinue the test and send the specimen to the laboratory for determination of volume and titration of free hydrochloric acid. The number of cubic centimeters of tenth normal sodium hydroxide required to neutralize 1 cc. of gastric contents times 100 equals the number of clinical units present. The presence of free blood or coffee-ground material should be noted.
- 5 If the sample develops a yellow color with Topfer's reagent, immediately inject an appropriate stimulus—histamine acid phosphate subcutaneously, 0.1 cc. per 10 kilograms of body weight, or insulin (regular) intravenously, 1 unit per 10 kilograms of body weight.
- 6 At 45, 60 and 75 minutes after injection completely empty the stomach by aspiration, collecting specimens in separate, labeled bottles and sending the samples to laboratory for estimation of volume and titration of free hydrochloric acid.
- 7 During the performance of the fractional analysis, the subject should be instructed to expectorate all saliva into a suitable receptacle.

- 2 The concentration of free hydrochloric acid in the stomach at any given moment represents an equilibrium between the effects of the acid liberating mechanisms and their opposing factors
- 3 The terms "hypo-acidity" and "hyper-acidity" have little significance in the light of modern concepts of gastric acidity
- 4 Certain features of fractional gastric analysis are of value, though limited, in the differential diagnosis of certain diseases of the gastrointestinal system
- 5 A study of the fasting gastric contents appears to be of significance equal to if not greater than a study of stimulated secretion
- 6 A simple, abbreviated technic of gastric analysis is advocated which furnishes the important information without undue strain on the patient or laboratory facilities and is therefore of practical value to the Army medical officer and practitioner alike
- 7 Insulin injected intravenously is a satisfactory stimulus to gastric secretion

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# THYROID DISEASE SEEN IN SOLDIERS OVERSEAS

MAJOR ORVILLE C. KING

MEDICAL CORPS, ARMY OF THE UNITED STATES

DISEASES of the thyroid gland were not common among soldiers admitted to a large hospital overseas during the past two years. However, three interesting cases presented themselves for diagnosis and treatment. The diagnoses in all three were unusual but were proved by pathological examination and/or clinical course. They emphasize the need for close cooperation between internist and surgeon in glandular disturbances, as evidenced in the fact that all three patients had their initial admission to the medical service.

## REPORT OF THREE CASES

**CASE I**—A white soldier aged thirty-four years, was admitted to the hospital December 30, 1942, with a diagnosis of hyperthyroidism.

**History**—The patient had been perfectly well until ten days prior to admission when he suddenly noticed pain with a sensation of fullness in the anterior aspect of his neck. He continued his duties until two days before admission when he had a chill and felt "feverish." He reported at "sick call" the following morning and was sent to the hospital. During the time interval he noticed a gradual increase in the size of his neck. There was no history of childhood diseases, but the patient had undergone tonsillectomy and adenoidectomy at eight years of age, he had pneumonia in 1931. Appendectomy was performed in 1940 for acute appendicitis.

The patient had lost 5 pounds during the past two weeks as a result, it was believed, of his working in the intense heat.

**Physical Examination**—The patient was a well nourished white male who appeared acutely ill. His temperature was 100° F., pulse 92 and respiration 20. Examination revealed a reddened inflamed pharynx with slight edema of the uvula. The neck appeared enlarged in the area of the thyroid gland. The gland itself was increased in size, uniformly smooth, markedly tender and indurated. This induration was so marked that it gave the impression of a stony hardness. The right lobe was larger than the left. There was no noticeable attachment to the overlying skin or deeper structures of the neck. The skin appeared normal overlying the gland. The cervical glands on the left were enlarged but not tender and were freely movable. The supraclavicular glands were enlarged bilaterally. No additional abnormalities were noted.

**Laboratory Studies**—**Urinalysis** Specific gravity 1.023 reaction basic, albumin negative, sugar negative, color straw-cloudy and 0 to 3 white blood cells per high power microscopic field. **Blood** Hemoglobin 70 per cent, red blood cells 3,620,000 white blood cells 8350 neutrophils 69 lymphocytes 21, eosinophils 2, basophils 2 and monocytes 6.

**Course**—An ice collar was applied to the patient's neck and he was otherwise treated symptomatically. His temperature varied between 101.4° to 99.4° F. until

the sixth day when it reached its maximum of 103.3° F. The pulse varied from 100 to a maximum of 118, respiration 18 to 24.

He was seen in consultation at this time by the author who confirmed the physical signs as described. The pharynx was still moderately injected and the uvula edematous. Chemotherapy in the form of sulfathiazole was begun and local treatment continued. Within twenty-four hours the temperature and pulse began to decline and seven days after the administration of the drug they were within normal limits. The thyroid gland gradually decreased in size but remained hard though less painful.

Complete blood counts taken during this interval showed a moderate leukocytosis but no increase in polymorphonuclear leukocytes. The basal metabolic rate taken eight days after admission was minus 9. Under the x-ray the lung fields appeared clear, the heart was not enlarged and there was no evidence of substernal thyroid.

On the fourteenth day following admission the patient's temperature again rose to 104° F and pulse to 100. The white blood cells numbered 8400, with 69 per cent of them polymorphonuclear leukocytes. At that time the pharynx appeared normal. The thyroid gland was smaller than on January 9, 1943, slightly tender but still firm. There was no attachment to the deep or overlying structures. We did not believe that there was any suppuration present but thought the temperature reaction was due to sulfathiazole and advised its discontinuance. Following the elimination of the drug the patient's temperature returned to normal and remained there during his stay in this hospital. The enlarged thyroid gland, though painless, gradually returned to its normal size and consistency within thirty-one days of admission.

*Comment*—The admitting diagnosis of hyperthyroidism was not substantiated either by history, physical findings or special studies. The history of chills and fever indicated infection. The physical findings added pharyngitis and uvulitis with enlargement and tenderness of the thyroid gland. Leukocytosis was present. It was the opinion of the attending physicians that the condition was one of infection of the thyroid gland with the origin in the pharyngeal area and an ultimate localization in the thyroid gland, with a resultant acute thyroiditis. While metabolism is usually increased in acute thyroiditis, in this instance the rate when determined eight days after admission was minus 9, a determination within normal limits. The rate continued to decrease, until on the seventy-second day following admission it was minus 17. This may be interpreted as an interference with the parenchymal cells by an infiltration of the products of infection, causing a decrease in the amount of thyroxin produced. Not until a cellular recovery took place was the thyroid gland able to return to its normal productive function, as was determined on the eighty-fifth day by a basal metabolic rate of plus 5.

This soldier fortunately made an excellent recovery and was able to return to full duty. In other cases complications such as suppuration with abscess formation have occurred, necessitating radical surgical drainage with resultant destruction of thyroid tissue, scar tissue re-

placement and myxedema. More frequent perhaps, following the acute stage, is the development of a chronic thyroiditis or Riedel struma

**CASE II.**—The second case of unusual thyroid disease to be presented is that of a white native of Massachusetts, aged twenty-eight years, admitted to the hospital August 13, 1942 complaining of a "lump in the neck."

*History of Present Illness*—This soldier first noticed a small lump in the region of the left lobe of the thyroid gland in October of the previous year. He saw a physician who after examination stated that it was nothing and "not to bother about it unless it grew larger." The patient was a member of the armed forces and on maneuvers at this time. He paid no further attention to this "lump" until July, 1942, when he was referred to the hospital for further study.

*Examination*—Examination revealed a discrete, firm irregular mass in the inferior pole of the right lobe of the thyroid. The gland itself was not otherwise enlarged and it was freely movable as was the skin over it. Laboratory studies were all within normal limits. The basal metabolic rate was minus 3.

*First Operation*—At operation on August 22, 1942, a small adenoma was found in the inferior aspect of the right lobe. A wide excision of the adenoma was performed and the tumor removed without difficulty. It was impossible at this time for the laboratory to perform microsectional studies and the specimen was sent to the mainland. Delay was encountered in obtaining the report and the patient was discharged to his outfit and ordered to return for examination every second week. He did so regularly and no further masses appeared. On October 5, 1942, a report and a prepared section were returned to us. The diagnosis was "adenocarcinoma of the thyroid with extension into normal tissue but not beyond area excised." This was confirmed by our pathologist and the patient was readmitted to the hospital on October 12, 1942. At this time the right lobe was seen to be slightly increased in size and one small adenoma was palpable in the left lobe. The gland itself was not attached to deeper structures. X-ray of the lung fields and skull failed to show metastasis.

*Second Operation*—At operation on October 14, 1942 the right lobe was increased about once its normal size and two small masses were present. The left lobe showed a small adenomatous mass in its lower portion. There was no adenopathy in the regional gland nor was there any gross evidence of extension into the surrounding tissues. A total thyroidectomy was performed without difficulty. The pathological diagnosis was papillary adenocarcinoma. The patient was transferred to a general hospital for roentgen ray therapy. Thyroid extract was given to him during his stay in the hospital. No follow up has been obtainable.

*Comment*—This patient had been assured that the "lump" in his thyroid was practically harmless and required no attention. It was only because a physician, at a later examination, was aware that adenomas of this character often undergo malignant change that the patient was referred to the hospital for its removal. The tumor appeared grossly benign, but the pathological diagnosis was adenocarcinoma. No one can deny the fact that the removal of this "lump" when first discovered would have been wiser. Bloodgood, Wilson, Graham, Lahey and others have stressed the fact that malignancy of the thyroid often exists first as a benign tumor. If the tumor is re-

moved during this stage or even during the early stage of malignancy, there is an excellent chance for prevention and/or cure. Once malignancy of the thyroid has involved the surrounding structures or spread beyond the capsule of the gland, therapy is practically hopeless even with combined surgery and x-ray. It should be emphasized that youth does not rule out the possibility of malignant changes. Malignancy must always be borne in mind when changes occur in glands which regress and progress during their active stage.

CASE III—The last case is that of a white sergeant, aged twenty-one years, who was admitted to this hospital April 9, 1943, complaining of pain and swelling in the region of the neck. He had been perfectly well until that evening when while wrestling with a fellow soldier he was grasped about the neck with a "head lock" which produced sudden pain in the anterior aspect of his neck. It was so severe that the wrestling bout was stopped. His neck started to swell immediately and he was brought to the hospital.

Examination at that time revealed marked swelling and tenderness of the entire thyroid gland with moderate ecchymotic discoloration of the overlying skin. Slight hoarseness was present and deglutition was painful. All other findings including temperature were within normal range.

It was believed that the patient had a contusion of the deep structures of the neck with hemorrhage into the thyroid gland. He was put to bed, an ice collar applied, sedation given and observation continued. Within five days the swelling subsided and the pain abated. Progress was sufficient to permit the patient's discharge in two weeks with but a slight residual thickening of the left lobe. He was returned to full duty.

On November 5, 1943, the patient was readmitted with the complaint of a sudden increase in the size of the left side of the neck. There were no other symptoms except slight elevation of the pulse rate. As the hospital was in the field at this time no basal metabolic estimations were obtainable. The patient was given Lugol's solution during his hospitalization. After ten days on the medical service the swelling had subsided to a degree and the pulse rate had returned to normal. He was discharged. He presented himself at the hospital four days later stating that the swelling on the left side of his neck had suddenly become larger. On that date (November 19, 1943) he was seen by me in consultation. The examination revealed nothing abnormal except a diffuse smooth cystic enlargement of the entire left lobe of the thyroid gland. This enlargement was attached neither to the overlying nor to the deep structures, and was freely movable.

It was recalled that the original injury to the thyroid gland with hemorrhage into the gland itself in April, 1943, had left some residual thickening of the left lobe. After several months the left lobe gradually increased in size. Was this cystic degeneration? We thought so. The sudden increase in size three days before the last admission might have been caused by a new hemorrhage, though no history of recent trauma was obtainable.

At operation November 20, 1943 the left lobe was found enlarged.

to twice its normal size. It was soft and smooth and was thought to contain fluid. A left lobectomy was performed without difficulty. Gross pathological examination of the specimen showed almost the entire left lobe filled with a dark sanguineous mucilaginous fluid and a small fresh blood clot. The surrounding tissue of the cyst was primarily fibrous in nature, with a small amount of compressed and degenerated thyroid tissue. The patient made an uneventful recovery and returned to full duty in the Air Corps ten days after operation. He has continued in good health to date.

#### SUMMARY AND CONCLUSIONS

Three cases of thyroid disease have been presented, each unrelated to the other and, with the exception of the case of malignant tumor, rather infrequent. These abnormal conditions were found in young adult soldiers in the second and third decades of life who had recently passed rigid examinations for overseas duty. They had all been under medical care on admission. The appreciation of the physicians in charge, of the possible complications during the course of such abnormal thyroid conditions led them to request surgical consultations. The combined efforts of both the medical and surgical services made for early diagnosis and proper therapy. They further demonstrated that surgery of the thyroid gland can be performed in the field, under necessity without undue risk to the patient by one familiar with such surgery.



# TREATMENT OF THE COMMON SKIN DISEASES IN AN ARMY HOSPITAL IN THE TROPICS

CAPTAIN THOMAS W CLARK

MEDICAL CORPS, ARMY OF THE UNITED STATES

Methods used to treat the common skin diseases in an Army hospital operating for over a year and a half in the South and Southwest Pacific will be described

The disorders most commonly encountered at these stations are epidermophytosis, dermatitis venenata, insect and mite bites Their characteristics are much the same as in the temperate zones but they tend to be more persistent and more severe Secondary infection is a complicating factor in nearly every case, and it is not too much to say that it is most often the infection and not the primary disease that leads to hospitalization

The general care of these patients is of great importance Difficult living conditions, a hot climate, and lack of appetizing food undoubtedly act to reduce men's stamina and resistance to infection It is not uncommon to find that a chronic ulcer started as a trivial scratch or a cellulitis as a simple fissure Rest, clean surroundings, well prepared foods, and vitamins in full doses are essential parts of the program of treatment There is no question that these patients do far better in a dry fly-proof building where the details of cleanliness, asepsis and general nursing care are easier to attend to than in the ordinary ward tent as it is set up in the field However, when only a ward tent is available, every effort is made to approximate the conditions of the better installation

The therapy as outlined in this paper is not original It consists of measures that have proved satisfactory after a year and a half of experience in a tropical climate Invaluable aid was obtained from the Manual of Dermatology by Pillsbury, Sulzberger and Livingood<sup>1</sup>

## EPIDERMOPHYTOSIS

Epidermophytosis is one of the most persistent enemies of our men In the tropics, where conditions are ideal for its development and spread, their difficulties with this disease are worse than in any other climate It incapacitates them despite all efforts with soap and water, boiled socks and foot powder The disease is frequently advanced and secondarily infected by the time the patients reach the hospital Over-treatment is the commonest error in management Strong solutions and strong ointments tend to irritate an already damaged skin, to hinder recovery, and even to aggravate the disease process The tendency

of doctors to adopt a routine course of treatment is often the reason why many cases of "athlete's foot" fail to improve. Treatment has to be individualized. It has to be cautious, and guided by the character and progress of the disease.

The acute stage, characterized by fissures, vesicles, broken blisters and denuded areas between the toes and under the feet, is generally complicated by secondary infection. Control of this secondary infection is the first and foremost aim of treatment. The patient is put at complete bed rest. The diseased areas are gently debrided of all loose epidermis and the tops removed from the large blisters every day. The feet are cleaned with a mild sterile soap solution. Warm soaks in a weak fungicidal solution are started. Potassium permanganate is usually available, and a solution of 1:10,000 (0.30 gm. in 3000 cc.) is quite strong enough. Solutions of stronger than 1:5000 are irritating and harmful. The feet are soaked for twenty minutes three times a day and dried. If the disease is widespread or if there is extensive secondary infection, continuous warm compresses of the same solution are to be preferred. Between soaks, the feet are left uncovered. In cases with extensive weeping the feet are exposed to dry heat under a cradle or in the sunlight to dry the skin and prevent maceration. When blisters or fissures between the toes are present, the opposing surfaces are separated with sterile powdered gauze. This again helps to prevent maceration of the skin. It is often desirable to put light sterile dressings over the affected areas during the night.

In many cases the secondary infection disappears and the original fungous infection subsides after two to four days of rest and soaks. The vesicles, fissures and macerated areas dry up and the thickened epidermis slowly peels off. The feet are kept clean and dry with foot powder and the patient is watched until desquamation is complete and all evidences of activity have disappeared. More often, the secondary infection subsides and the vesicles and blisters of the acute epidermophytosis are replaced by patches of thickened epidermis, with scaling and oozing from under the patches. A few more days of soaks with potassium permanganate solution sometimes control this condition. If no more improvement occurs within this time one of the dyes in solution such as Castellani's paint\* or 2 per cent gentian violet in 70 per cent alcohol is applied. Frazer's solution† or tincture of iodine is

#### Castellani's Paint

Saturated alcoholic solution of basic fuchsin	10.0
Aqueous solution of phenol 5%	100.0
Filter and add	
Boric acid	1.0
After two hours, add	
Acetone	5.0
After two hours, add	
Resorcin	10.0

Keep in dark stoppered bottle

#### †Frazer's Solution

Salicylic acid	2.0
Benzoic acid	2.0
Tincture of iodine	10.0
Spirits of camphor to make	60.0

also effective at this stage. It was found best to start off with a quarter to one-half strength solutions and to increase slowly until the full strength is applied twice daily. If any evidence of irritation appears, the medications are stopped.

Most cases clear up entirely with potassium permanganate soaks alone or with potassium soaks followed by one of the medications mentioned above. A few enter a chronic stage characterized by thickened plaques of epidermis, scaling and fissuring. These lesions are resistant to treatment and characteristically relapse time and again. It is important to treat them cautiously because they are apt to flare up acutely when irritated. Solutions containing iodine from 1 to 7 per cent in strength often yield good results. These are painted on the lesions twice a day. If no improvement with iodine takes place within two weeks or if iodine irritates the lesions, other medications such as Castellani's paint or Whitfield's ointment are tried. Many weeks of continuous treatment are sometimes necessary before the lesions heal completely.

Ointments have been widely used against all stages of this disease. There is no question that they are valuable at times, but by and large they are best avoided in the tropics. They favor the spread of secondary infection when applied over contaminated lesions. Whitfield's ointment is very valuable for softening up the dry scaling epidermis of the subacute and chronic stages. When applied it is rubbed into the lesions thoroughly. No dressings are placed over it. It is never used in the acute stage or when secondary infection is present. Treatment is started with mixtures of a quarter to half strength in order to avoid irritation of the skin, and full strength is reached gradually. Sulfur ointment proved to be of no value in this disease. Ammoniated mercury was mildly antiseptic but relatively ineffective against the fungi of epidermophytosis.

Dermatophytids on the hands and ears are common complications of epidermophytosis of the feet or groin. They are characterized by vesicles, scaling, eczematoid patches, fissures and varying degrees of erythema, and are very similar to other dermatoses. They are often far more prominent than the primary lesion. The commonest error is to overlook the primary lesion on the foot or the groin and to mistake the "id" for a separate and distinct disease. The uncomplicated "id" will heal only when the primary disease is cured, therefore when confronted with such lesions it is important to look for epidermophytosis elsewhere on the body and to treat it as described above. The "ids" are treated symptomatically with mild medications. Potassium permanganate soaks are useful for drying up the oozing from broken vesicles. When there is much scaling and fissuring present, boric acid ointment or petroleum jelly is used to soften the lesions. When secondary infection is present it is treated as described above.

After the disease has been controlled and the patient is ready for

duty, he is rehearsed in the care of his feet with emphasis on the use of soap and water and foot powder. His shoes are fumigated by placing them in an air-tight container for twenty-four hours along with a sponge soaked in 30 per cent formaldehyde. Following this they are aired for twenty-four hours in the sunlight. The patient is told that recurrences may take place no matter how conscientious he might be and that at the first sign of renewed activity he should report for treatment.

#### DERMATITIS VENENATA

The tropical forests are full of plants and trees whose leaves and barks contain substances irritating to the skin. Contact with these substances results in conditions varying from momentary burning and reddening of the skin to the severest forms of dermatitis in which all layers of the skin become damaged. The very nature of the lesions increases greatly the likelihood of secondary infection unless care is taken to avoid contamination. Itching is usually intense and distressing to the patient. Treatment demands all the ingenuity at our command. As an example of the difficulties encountered the following case is cited.

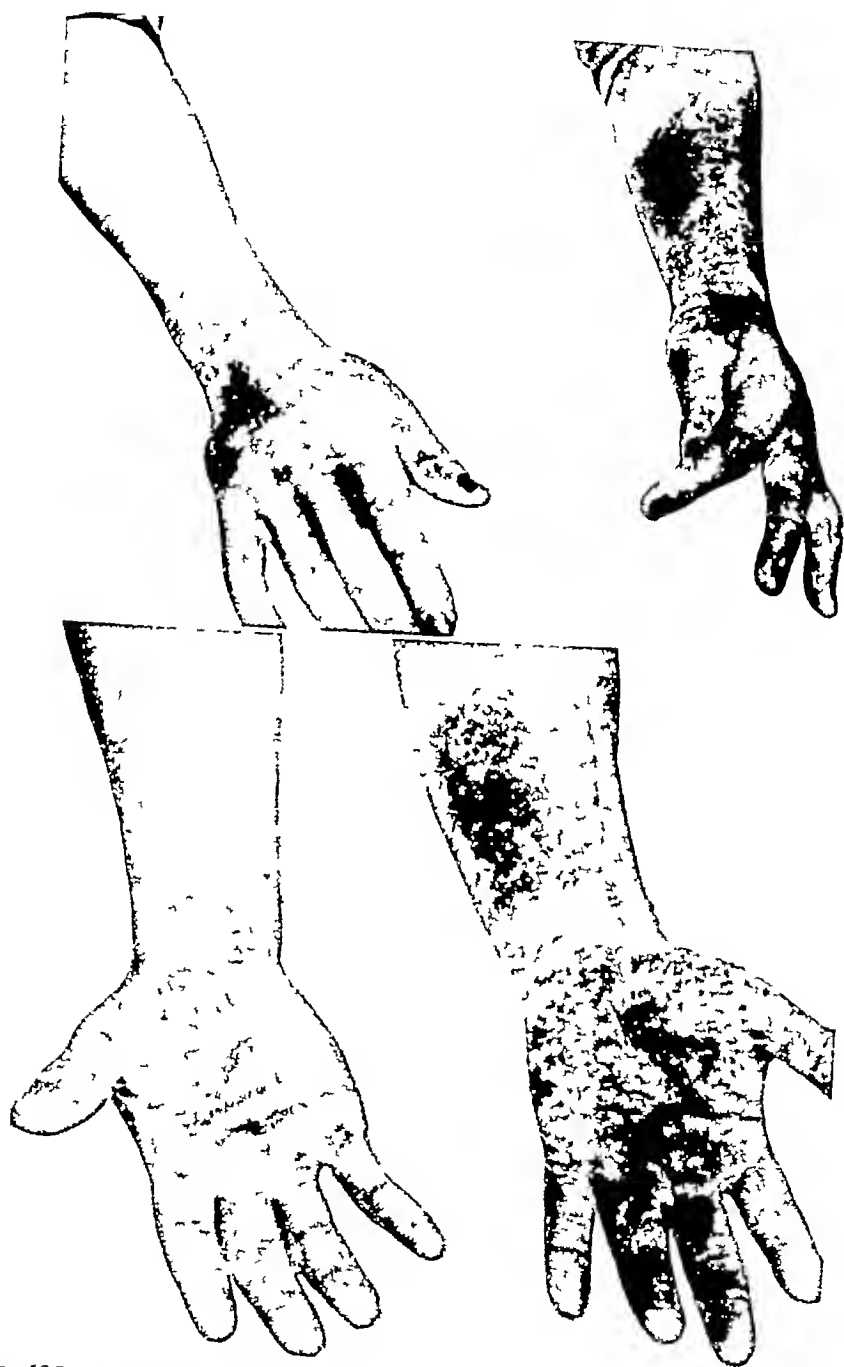


Fig 135—Appearance of the hands and arms of W O, a private in the Marine Corps, on admission to the hospital. The discoloration was due to potassium permanganate soaks applied before admission. Large blebs filled with pus and loose shreds of epithelium can be seen on the palms and fingers of both hands. The denuded and ulcerated areas are less distinct but visible as pale patches on the left hand and wrist.

nued and 2 per cent gentian violet in 70 per cent alcohol was painted over the hands and forearms. In a short time several of the infected areas flared up. The gentian violet was stopped and warm compresses followed by sulfadiazine ointment were resorted to once again. In three more days, all evidence of infection had disappeared. Scattered spots continued to weep clear serum. These were touched with gentian violet every day until they healed. Gradually new epithelium grew over the denuded areas. Twenty six days after admission the patient was discharged to duty.

Most of the patients with dermatitis venenata who are admitted to the hospital exhibit severe skin damage such as that described above. The condition of the skin is similar in many ways to a first or second degree burn and the same principles of treatment are followed. Sterile instruments for debriding, sterile solutions for washing, sterile ointments and gauze for dressings are all essential for the work.

From the start, the diseased areas are protected with sterile coverings. First, the lesions are carefully debrided of all crusts and loose epidermis. The tops of blisters are removed. The involved areas are cleaned with green soap, sterile water and alcohol and then covered with a sterile ointment spread thinly. Boric acid ointment and petroleum jelly both are satisfactory for this purpose. Gauze impregnated with either ointment and autoclaved affords a neat method for applying these medications. The ointment not only protects the damaged skin from infection but also soothes the burning and itching that often causes great distress.

When secondary infection is present it is treated promptly and according to its severity. If it is a simple superficial infection, the above regimen is usually enough to control it. A sulfonamide drug is sometimes added to the protective ointment. Five per cent sulfadiazine in a water-soluble base\* is frequently used with excellent results. If a widespread pyoderma has developed with an underlying cellulitis and fever, more vigorous treatment is prescribed. The lesions are carefully debrided and cleansed as before. Warm saline compresses are applied for an hour every four to six hours. The moist compresses help to clear away the pus and crusts and also to combat the cellulitis. Between soaks the lesions are covered with dry sterile dressings. When the dressings are removed they are soaked off in order not to damage any regenerating epithelium. The compresses are continued until the infection is well controlled. Generally, twenty-four to thirty-six hours are sufficient. Then ointment and gauze dressings are applied as described above. As long as they are present, oozing and crusting lesions are covered in order to avoid the recurrence of infection.

The more severe cases require sulfathiazole or sulfadiazine by mouth. The usual course prescribed for each drug is 2 gm immediately,

\*Water-Soluble Bases

1 Aquifer 2 Hydrogenated Vegetable Fat.

Other ointment bases may be found in the Manual of Dermatology.<sup>1</sup>

1 gm every four hours for forty-eight hours, and then 1 gm four times a day until the infection improves Sodium bicarbonate is given in equal amounts with each dose of the sulfonamide The common precautions are observed, and at the first sign of an untoward reaction the drugs are stopped

Medications which form eschars over excoriated surfaces have often been applied on a weeping dermatitis Tannic acid and gentian violet were both used in the case described above However, they are not recommended in this disease The eschar may seal over an area of secondary infection and encourage its spread, as in this case The eschar had no effect on the course of the disease and the protection it afforded to the denuded skin could have been given better and more safely with a bland ointment and bandages

Itching is generally present in all stages of this disease It causes great distress and is difficult to control Scratching is an important source of secondary infection and must be prevented In the milder cases with little excoriation of the skin, the lesions are treated frequently with antipruritic lotion and covered with sterile dressings for protection A clean and effective lotion is the following

R. Phenol	20
Glycerine	150
Lime Water	1200

Ointments are also soothing and helpful against itching Even more effective in some patients than the lotions and the ointments are phenobarbital, aspirin and codeine These are used freely

Corn starch and oatmeal baths are effective in relieving the intense itching in a few patients with extensive dry exfoliating lesions on the trunk and thighs Baths are never used in the presence of secondary infection One half to 1 pound of cornstarch is ample for a 40-gallon tub of water Warm baths are better tolerated than cold Even in a hot climate patients become chilly if left in the tub much over thirty minutes *It has been found best to limit the procedure to twenty to thirty minutes and to repeat it two to three times a day*

#### INSECT AND MITE BITES

Fleas, mites and mosquitoes are present in great numbers and their bites are a constant source of annoyance to the troops Mite bites on the ankles and legs are particularly troublesome Secondary infections from scratching these lesions are common and persistent and often require hospitalization for treatment

Measures for the prevention of bites are taken whenever possible Orders were issued to apply insect repellents liberally over the exposed parts Formula 612, made by the National Carbon Co, Inc, is in our experience the best of these Smeared frequently over the

ankles and legs, "612" is very effective against mite bites. Sulfur preparations, recommended against the "chiggers" of the Southern United States, have not proved so satisfactory. Protective clothing is worn at all times. Beds are aired and sprayed frequently. While these measures do not completely eliminate the bites, they reduce the number.

Treatment of insect bites is directed toward relief of the itching, thus reducing the incentive to scratch. Antipruritic lotions and pastes are helpful, although they are messy and their effects last only an hour or so. Nevertheless, they are well worth trying when an individual is suffering a great deal. The following lotion proved very useful.<sup>1</sup>

R. Zinc Oxide	25.0
Talc	25.0
Bentonite or kaolin	5.0
Camphor	5.0
Menthol	0.5
Water	30.0
Alcohol, 95 per cent	30.0

Some persons cannot control their scratching and in these it is necessary to cover the bites with a protective bandage.

*Scratch infections* are common and are extremely resistant to treatment. They vary anywhere from small pustules to furuncles and ulcers. If the lesions do not heal after a week of dispensary care, the patient is hospitalized and the same care is given as has been described for other secondary infections. The patient is put to bed. The lesions and surrounding skin are cleansed well with green soap, sterile water and alcohol. If the infection is severe and cellulitis is present in surrounding tissue, continuous hot saline compresses are applied for about twenty-four hours. Then the lesions are covered with a sterile ointment or gauze impregnated with an ointment. Sulfadiazine in a water-soluble base, boric acid ointment and petrolatum are all satisfactory for this purpose. The use of adhesive tape on the skin is avoided because it favors the development of satellite lesions. If no improvement occurs in a week with the above treatment, a full course of sulfadiazine or sulfathiazole is given by mouth. Experience shows that these infections once established tend to persist indefinitely even in the milder forms until the patient is put to bed and the lesions are protected from dirt and trauma.

#### X RAY

Facilities for the use of x-ray therapy were of necessity<sup>1</sup> our experience with this form of treatment was not great. In it was used most often against the chronic forms of epidermophy. The results were disappointing, although it was effective against secondary infections that complicated this condition. Second-



fections can be managed by less risky means, and therefore the x-ray was not considered for routine treatment

### CONCLUSION

The skin diseases most commonly found in soldiers on duty in the tropics are epidermophytosis, dermatitis venenata and insect and mite bites. Secondary infections sometimes complicate these conditions and cause prolonged hospitalization. Strong and irritating medications often aggravate the acute process. Good general care, strict adherence to aseptic surgical technics and the judicious use of local therapy are important factors in the treatment of these diseases.

### REFERENCE

- 1 Pillsbury, D. M., Sulzberger, M. B., and Livingood, C. S. *Manual of Dermatology*. Issued under the auspices of the Committee on Medicine of the Division of Medical Science of the National Research Council. Philadelphia, W. B. Saunders Company, 1942.

# THE ANXIETY NEUROSES MANIFESTED BY GASTRO INTESTINAL SYMPTOMS

CAPTAIN ALEXANDER RUSH

MEDICAL CORPS, ARMY OF THE UNITED STATES

In an Army hospital during the first year of war in the South Pacific, many interesting gastro-intestinal problems were encountered. In general these were conditioned by (1) the climate and living conditions, (2) the previous preparation of the individual soldier for overseas duty and (3) the early deficiencies in selecting soldiers for combat service. In order of frequency, the diseases met with were (1) dysentery, (2) jaundice, (3) the gastro-intestinal neuroses, (4) peptic ulcer, (5) gastro-enteritis and (6) gastritis. In diagnosis and treatment, the gastro-intestinal neuroses furnished perhaps the greatest difficulty. The problem revolved around the separation of those patients with symptoms due to definite organic disease from those with symptoms due to emotional disturbances.

**Incidence**—It is estimated that approximately 25 per cent of all hospital admissions were for disorders of the gastro-intestinal system. It is interesting that of all the types of psychoneurosis seen, the most frequent were those associated with altered function of the digestive tract.

## CLINICAL PICTURE

**History**—The clinical picture of the gastro-intestinal neuroses is extremely variable. The victims sleep poorly, experience frequent bad dreams, are easily fatigued and depressed. This uneasy emotional state is reflected in all kinds and degrees of digestive complaints, ranging from poor appetite, coated tongue, sensation of lump in the throat, belching, heartburn, bloating, nausea, vomiting, gnawing, burning sensations in the epigastrium to rumbling and gurgling, abdominal cramps and "constipation." The complaint most frequently encountered is migratory lower abdominal cramps occurring shortly after the ingestion of food and relieved spontaneously within an hour or following a bowel movement. Feelings of fullness on eating and rumbling and gurgling frequently accompany these symptoms. The two next most frequent complaints are nausea and vomiting during or shortly after eating, and burning, gnawing epigastric pain that may be indistinguishable from that of peptic ulcer. It is a characteristic feature that in spite of these severe gastro-intestinal symptoms, rarely do these patients show evidence of malnutrition or loss of weight.

**Physical Examination**—Tenderness over the course of the large bowel and a palpable, tender sigmoid may be present on physical examination. These signs are demonstrable in about one third of the patients.

**X-ray Examination**—In contrast to the experience of some observers, this type of study in our hands seldom furnished evidence that could be considered diagnostic of a psychogenic gastro-intestinal disorder. The chief value of x-ray study lies in providing negative evidence of an organic lesion and in having, in many instances, a beneficial psychological effect.

**Stool Examination**—Repeated stool examinations failed to reveal any consistent abnormalities characteristic of functional disturbances of the digestive tract. The presence of mucus, commonly associated with the diagnosis of irritable or spastic colon, was noted in 25 per cent of our patients with functional digestive disorders. This compares with 23 per cent observed in a comparable group of patients with peptic ulcer. This difference can hardly be considered significant. Just as in the case of x-ray studies, the greatest value of routine stool examination lies not so much in the prospect of providing positive evidence of a functional disorder as in ruling out other organic diseases that produce similar symptoms and signs.

**Proctoscopic Examination**—The appearance of the mucosa on proctoscopic examination presents little that is characteristic. The presence of mild hyperemia and mucus is suggestive but it is not a constant finding. The detection of bits of undigested food such as carrots that have been eaten at the preceding meal is of some value as indication of hypermotility. The initiation of the patient's characteristic distress when the proctoscope is introduced occurs in a surprising number of instances.

**Army General Classification Test**—For those not familiar with it, the Army General Classification Test<sup>1</sup> is a form of intelligence test designed to determine the individual ability of each soldier to learn his duties. On the basis of his score, each soldier is placed in one of five broad categories called groups. Group III contains the largest proportion of all men in the Army. It represents the "average learner." On the one side are Groups I and II which embrace a small percentage of "very rapid learners" and a larger percentage of "rapid learners." On the other side the picture is reversed, Groups IV and V containing the "slow" and the "very slow learners" respectively. It is significant that of a large group of gastro-intestinal neuroses,<sup>2</sup> not a single case fell in Group I, one case fell in Group II, while twice as many as would normally be expected were found in Groups IV and V. The results of these tests furnish information helpful in estimating an individual soldier's ability to make the adjustments necessary in Army service and are of some prognostic value when considered in conjunction with the patient's history and his personal record.

#### DIAGNOSIS

The diagnosis of a gastro-intestinal neurosis is facilitated when (1) a history is obtained of abdominal distress which may include many

diversified symptoms but is commonly characterized by the production of intermittent migratory, lower abdominal cramps upon the ingestion of food, (2) anxiety or other manifestations of an unstable personality are apparent, (3) tenderness over the course of the large bowel and a palpable sigmoid are found on physical examination, (4) no organic lesion can be demonstrated by x-ray or other studies to account for the clinical picture

#### DIFFERENTIAL DIAGNOSIS

**Peptic Ulcer**—The number of patients suffering from a functional digestive disturbance and presenting symptoms indistinguishable from peptic ulcer is small but they present a difficult problem in differential diagnosis. The *clinical history* is often of some help since in a functional disorder the periodicity characteristic of ulcer distress is usually lacking. In a chronic gastro-intestinal neurosis, the symptoms are intermittent and unpredictable rather than periodic. Moreover, on physical examination the sharply localized tenderness characteristic of ulcer differs from the widespread tenderness of irritable colon that is frequently present over the entire course of the colon.

Further to rule out peptic ulcer several procedures may be employed, none of which by itself is adequate and all of which must be interpreted in terms of the patient as a whole. *Gastric analysis* has proved to be of doubtful value except in those instances in which the content of the fasting stomach exceeds 120 cc and reveals a value for free hydrochloric acid higher than 25 clinical units. Such figures are seen in less than a quarter of those patients suffering from a gastro-intestinal neurosis while they are associated with peptic ulcer in over 75 per cent of cases.

When the positive signs of ulceration or persistent deformity can be demonstrated, *x-ray examination* is most helpful in the differential diagnosis. It must be borne in mind, however, that the mere absence of these signs in itself does not rule out the diagnosis of peptic ulcer. The percentage of positive x-ray findings in the presence of peptic ulceration varies widely in different clinics and with different techniques.

Under conditions where gastric analysis and gastro-intestinal x-rays are unable to confirm the diagnosis of ulcer, two additional procedures have been found helpful. Palmer and Heinz<sup>3</sup> have called attention to the fact that in the presence of a fresh lesion, the instillation into the stomach of 200 cc of 0.3 per cent (0.1 normal) hydrochloric acid induces typical ulcer distress which can be relieved promptly by aspiration of the stomach contents and the introduction of an equivalent volume of a 2 per cent sodium bicarbonate solution. Patients with functional disturbance of the gastro-intestinal tract may complain of vague discomforts when this procedure is carried out but never of the typical distress described in those individuals suffering with an active ulcer. Finally, a fo-

tained score of 128 (Group II) "rapid learner," in the Army General Classification Test Gets along well with others but is full of nervous energy and attacks every problem as if his life depended upon it.

*Physical Examination* Slight tenderness over the frontal sinuses Thyroid not enlarged Lungs clear Heart normal Blood pressure 130/82 Pulse 70 Abdomen liver and spleen not palpable, colon not palpable or tender, no other organs or areas of tenderness noted

*Impression* Peptic Ulcer?

*Course* Diagnostic studies included a complete blood count which proved to be entirely within normal limits Urinalysis was negative Gastric analysis showed a fasting stomach content of 107 cc with a free hydrochloric acid level of 27 clinical units Gastric secretory response at the end of one hour and a half to 8 units of insulin intravenously resulted in a volume of 98 cc with a free hydrochloric acid content of 77 clinical units Stool examination was negative X-ray report "Fluoroscopic examination of the esophagus was negative No defect of the stomach was seen Peristalsis and motility were normal The stomach was empty at the end of four hours The head of the meal was in the transverse colon" Acid test No pain at the beginning of the test. Levin tube passed and stomach aspirated, and 200 cc of 0.3 per cent hydrochloric acid introduced through the tube No pain resulted during a period of 15 minutes Acid was then removed After an interval of 15 minutes during which there were no unusual sensations, 200 cc of 2 per cent solution of sodium bicarbonate was introduced through the tube At no time was any distress described The test was interpreted as negative as far as indicating the presence of a fresh active ulcer The patient was placed on a bland diet with 15 drops of tincture of belladonna a half hour before each meal, and was discharged to duty three days after admission Within three weeks all symptoms had disappeared and except for one brief period of distress which was promptly relieved by diet and belladonna, the patient has remained in good health

*Final Diagnosis* Functional Gastro-intestinal Disturbance Symptoms resembling peptic ulcer

*Comment*—This case is presented because it illustrates the course of events in a mild disturbance It also demonstrates the misleading clinical picture of peptic ulcer that sometimes is encountered and the various steps taken to eliminate that organic disease from the diagnosis Of significance, too, are the factors contributing to a successful outcome in this patient These were, first, the relatively short period of time that the symptoms had been present, second, the mildness of the distress, third, the emotional response was due to a purely local situation, fourth, a rapid diagnosis was made and treatment consisting of rest, explanation, reassurance, coupled with dietary and therapeutic measures were instituted without delay On such a program the danger of the development of a chronic disease can be minimized

*CASE II*—This man, a 27-year-old private first class, was admitted December 22, 1942, and discharged January 3, 1943 He was readmitted January 15, 1943, and transferred January 23, 1943

*Chief Complaint* Pains in stomach for past two years.

**History of Present Illness** This patient entered the service March 20, 1941. Prior to that time he worked as a laborer and enjoyed excellent health until about six months before induction. He recalls that it was just about this time that he learned that he had been selected by his local draft board. Shortly thereafter he began to be troubled with "indigestion" characterized by sensations of fullness after meals and sour eructations. These symptoms would come on at irregular intervals. About one week after arrival on this island, they became practically continuous. He started to vomit small amounts of sour material immediately after eating and would experience "heartburn" for about an hour and a half. In addition to these symptoms, he would sometimes be awakened about midnight with a burning sensation in the pit of his stomach. This distress likewise was relieved by the taking of water. His bowels moved regularly without laxatives, and his stools appeared normal. During the course of the preceding two months, he estimates he lost about ten pounds in weight.

**Systemic Review.** Nothing remarkable.

**Past Medical History** No serious illnesses or operations. Tonsillitis followed by tonsillectomy as a child.

**Family History** Father and mother well. There is a sister who has "stomach ulcers."

**Social History** Single. Gets along fairly well with others. Army General Classification Test score 98—Group III, average learner.

**Physical Examination.** Positive findings: a liver just palpable on deep inspiration and slightly tender; moderate generalized tenderness in the epigastrium palpable, tender, sigmoid colon.

**Impression.** 1. Functional Gastro-intestinal Disturbance

2. Possible Peptic Ulcer

**Course** A complete blood count and urinalysis were negative. Gastric analysis showed a fasting content of 114 cc. with a free acid level of 14 clinical units. X-ray examination revealed a normal pattern but at the end of four hours the head of the barium meal was in the rectum. Proctoscopic examination disclosed the presence of a mild proctitis.

When the patient was placed on a bland diet, the symptoms were partly but not entirely relieved. After a reassuring talk, during which the patient's findings were reviewed, he was discharged to duty albeit with some misgivings. As was customary in these cases, a letter was sent to his organization containing a summary of findings, diagnosis and treatment and requesting that, should it become necessary to hospitalize the patient again because of continued distress, an estimation by an officer as to his ability to perform his regular duties be supplied for guidance in ultimate disposition.

On January 15, 1943, the patient was readmitted to the hospital complaining of the same distress and accompanied by the following note from his battalion surgeon:

"1. Patient has been followed for twelve days on a modified Sippy regimen consisting of Tr. of Belladonna minims X t.i.d., a.c., and powders (Bismuth subcarb., Mag. Oxide, Calcium Carbonate), interval feedings of milk, broth, bread, rest and light duty. Weight loss continues as do gastric symptoms.

"2. In his present state, whether wilfully or subconsciously induced, soldier is no asset to his organization and is in reality more of a detriment as he cannot be counted on. Whether he really cannot work or has made up his mind not to, should be investigated psychiatrically in the absence of gastroenterologic demonstration on last admission."

In the light of this information and our conclusions as to the nature of this soldier's disability, it was recommended by a board of medical officers that he be returned to the interior for further evaluation

*Final Diagnosis* 1 Functional Gastro-intestinal Disturbance Irritable Colon  
2 Chronic Anxiety State

*Comment*—This case illustrates several interesting points. While unfortunately there is no detailed information as to the patient's early life, his occupation and Army General Classification Test score suggest that this man was not among those who learn quickly. The fact that he dates the onset of his symptoms to a time shortly after he had received word that he would be inducted is significant and suggests a possible relationship to the development of a chronic anxiety state. During this stage the symptoms were not severe and were transient. Arrival at his final destination overseas suddenly presented as a further source of anxiety new and more exacting conditions of life. Almost immediately his symptoms were increased and became continuous.

With regard to symptomatology, the variety of complaints is characteristic. While the story of night pain is suggestive of ulcer, the typical periodicity of ulcer pain is absent. The loss of weight is a little unusual but when it does occur it is customarily seen in those who have anorexia, nausea and vomiting.

As far as clinical and laboratory findings are concerned, a tender palpable sigmoid colon is rather typical. The fact that the head of the barium meal was in the rectum four hours after ingestion is an indication of increased irritability and motility of the digestive tract. In passing it should be said that this is one of the few instances where x-ray studies furnished positive evidence of disturbed function in a patient with gastro-intestinal neurosis.

With regard to treatment, the unsatisfactory response of this patient rendered the possibility of a successful return to duty very unlikely. This is the usual course of events in these cases.

This case also illustrates the mutual benefits to be derived from close liaison between hospital and medical officers in the field. The ultimate disposition in this case was facilitated by the information obtained from his parent organization.

**CASE III**—This man, a 27-year-old private first class, was admitted January 12, 1943.

*Chief Complaint* Cramps in the abdomen after eating.

*History of Present Illness* This is the patient's third hospital admission for the same complaints, which have been present over a period of at least two years. His distress is characterized by lower abdominal cramps, coming on shortly after the taking of food, lasting an hour or more, relieved by bowel movement. Stools move with difficulty and for that reason the patient has been in the habit of taking some sort of laxative about every three or four days. Appetite is only fair. No nausea or vomiting. No loss of weight.

*Systemic Review* Nothing remarkable.

*Past Medical History* "Inflammatory rheumatism" at eighteen years, confined to bed for six months. All joints of the extremities were affected at one time or another, starting in the ankle.

*Family History* Mother died of tuberculosis when the patient was five years of age. No details concerning health of other members of family are available.

*Social History* See below Single. Score in Army General Classification Test 66 (Group VI) 'very slow learner' Completed eighth grade in school

*Physical Examination* Patient appears apathetic slow to answer and seems to have difficulty in maintaining attention. Except for a slight presystolic apical murmur in the standing position no abnormal physical findings are present.

*Impression* Functional Disturbance of the Gastro-intestinal Tract. Irritable Colon

*Course* Diagnostic procedures were carried out with the following results. A complete blood count was entirely within normal limits. Urinalysis was negative. Stools were normal X ray report "Chest lung fields are clear; heart is not enlarged transversely Gastro-intestinal series normal gastro-intestinal tract." Gas-tric analysis furnished results that were well within normal limits. This patient was placed on a bland diet and tincture of belladonna, 15 drops before each meal, and elixir phenobarbital, 1 dram four times a day, which effected some subjective improvement.

During his third and last admission the patient wrote a suggestive note to a nurse which led him into considerable trouble. This occurrence prompted further questioning which revealed a very interesting psychological history bearing a definite relation to his disability and furnishing an illuminating illustration. The patient's mother died when he was five years old. He and his sister went to live with their grandmother. He did poorly in school. He stated that his "conduct was exemplary" but he "never ventured anything" and "that's my trouble." However, he claims to have had a few friends and managed to get along fairly well until about two years before his present admission when he first began to have symptoms. At this time he was working as a "bus boy" in a city hotel where he was teased incessantly by his companions. He became so upset by their treatment that he gave up his good job. This was especially disappointing to him as he was trying to make enough money to buy a new car and thus appear desirable to his girl. But it seemed to him that he was never able to "make the grade" without someone else's help. This need he stated, was felt most acutely. He then entered a period of emotional depression and even tried three times, unsuccessfully to commit suicide. Since then he has felt completely inadequate and fearful of everything and has experienced increasing difficulty in getting along with his associates. They apparently perpetually tease him to the point of exasperation over his inability to cultivate any women friends. "That's the trouble. I never feel that I am a man. I still feel like a little boy." Unfortunately, this patient was transferred to another hospital and dropped from sight.

*Final Diagnosis* Psychoneurosis

Functional Gastro-intestinal Disturbance

Irritable Colon

*Comment*—In contrast to Case I, this man's symptoms were severe and of long duration. His entire childhood had been marked by feelings of insecurity and by failures in his attempts at normal social adjustments. His internal emotional conflicts increased to the point where



they began to be reflected in bodily symptoms. These disturbed bodily functions in a way seem to have helped him to explain his frequent shortcomings and as a result they became an essential part of his psychological make-up. When he was selected for the service, the strain of trying to meet the new conditions of Army life, with its attendant homesickness, regimentation, apparent lack of understanding on the part of his officers and fellows coupled with his anxiety for the future, contributed greatly toward exaggerating an already established psychoneurotic behavior pattern. In the face of these circumstances a successful therapeutic result was not likely. The only sensible course was to remove this man from his organization for further psychiatric study and disposition.

In concluding the discussion of this case, it should be emphasized that not all the gastro-intestinal neuroses present such a vivid history. Yet the childhood insecurity, the seemingly unbridgeable gap between the longing for dependency and the aspiration for self-sufficiency, as Alexander has pointed out, seems to be characteristic of many of the gastro-intestinal neuroses.

#### TREATMENT

The treatment of the established gastro-intestinal neurosis divides itself naturally into three parts.

- 1 A careful history and physical examination by a physician who makes a point of lending a sympathetic ear not only provides essential information but aids in gaining the confidence of the patient without which no form of treatment will be successful. Whatever diagnostic procedures are indicated should be planned so that they will be completed as expeditiously as possible, thus holding the patient's interest and insuring his continued cooperation and confidence. As soon as the reports are available, the results should be carefully reviewed with the patient, their significance explained if possible, and any questions frankly answered. If no important abnormalities have been found, every effort to reassure should be employed, emphasizing that, although the symptoms are very real, they are not due to any demonstrable organic disease such as cancer, ulcer or gallstones. An attempt can often be made to develop in the patient some understanding of the intimate relationship of such common emotions as anxiety, fear, resentment to disturbances of digestion and some insight into his own condition and his habit of "getting his bowels in an uproar" when these feelings come into play. This approach may be especially helpful where the anxiety state results from a conflict between the instinct of self-preservation and the fear of dishonor and disgrace.
- 2 Specific measures are indicated consisting in a soft bland diet and elimination of known offending foods as well as raw fruit, fruit juices, uncooked vegetables and carbonated drinks.

3 In conjunction with this dietary regimen, some form of sedative to relax the patient may be given along with some form of antispasmodic to relax the bowel. A half an hour before each meal and at bedtime  $\frac{1}{2}$  grain of phenobarbital may be given along with tincture of belladonna in gradually increasing doses (starting with 15 drops and each successive day adding an additional drop to each dose until the limit of tolerance is reached as indicated by the onset of tachycardia, excessive drying of the mouth, flushing or disturbed vision). If possible the dosage is maintained at that level which affords the maximum of relief and the minimum of toxic reaction.

#### COMMENT

Several factors are involved in the development of the gastro-intestinal neuroses among soldiers. Our attention centers first on the influence of popular conceptions as to dietary habits. The present generation of soldiers, in contrast to those of the last war, have been bombarded since early childhood by parents and public alike on the dire consequences of "hyperacidity," "sluggish liver" and "constipation." Billboards, street car advertisements and radio have all luridly directed attention to the intestinal functions. As a result, the present generation has had every incentive to focus its ills in the gastro-intestinal tract. The seeds of a "mass neurosis" have been widely disseminated. While this factor alone probably does not directly activate a neurosis, it may well influence the character of the somatic symptoms that appear.

Another factor totally unrelated to the above, which has a bearing on the number of functional disorders has been the failure to recognize and eliminate the psychoneurotics and incipient psychoneurotics in the selection of men for overseas duty. The troops upon whom our observations have been made were among the first group of selectees. These men were hastily inducted into the Army in such large numbers that little opportunity was afforded to assign them according to their psychological qualifications as well as to their physical fitness and special aptitudes. The result was that there were included among combat troops an unnecessarily large number of men who were psychologically in no way fitted for the type of duty assigned to them but, on the other hand, might have been useful on the home front in jobs more suited to their emotional capacities. The expense to the government in terms of training, transportation and hospitalization of such men is difficult to measure but it must be high. Recognition of these misfits should be facilitated by the fact that the majority of soldiers suffering from functional disturbances of the gastro-intestinal tract are found to be among the poor learners and among those who have made unsatisfactory adjustments to the ordinary problems of civil life. When they enter the service, the stresses and strains of regimentation, new standards of living, new responsibilities, new

and new fears, all tend to bring to the surface and accentuate the physical equivalents of their poorly integrated emotional systems

Complicating the situation of these first selectees has been the fact that many of these men entered the service with the belief that as soon as their year was up they would be returned to civil life. While their country was not actually at war when the year rolled around, nevertheless conditions were such that these men were kept in the service in spite of earlier assurances to the contrary. This turn of events led to strong feelings of distrust and resentment in some individuals which were carried with them overseas. The will to fight was not there. If the nation had been actually at war at the termination of their tour, probably these feelings would never have arisen. Regardless of the precise origins, however, the first problem of the gastro-intestinal neuroses is the separation of those symptoms due to definite organic disease from those due to various disturbed emotional states.

The second problem in these neuroses centers about the proper treatment and disposition of the patients. A course should be chosen that serves the best interests of the Army and at the same time does not seriously neglect those of the individual. It has been our experience that the gastro-intestinal neuroses can be divided for the purposes of treatment into two broad categories based largely upon the chronicity and severity of symptoms. In one group the symptoms are mild and the result of a purely local situation that often can be remedied. These men are benefited by a rapid diagnosis and prompt treatment in the form of explanation and reassurance supplemented by symptomatic measures. On this program, almost 90 per cent are able to return to their units and maintain their efficiency. The remainder are the confirmed psychoneurotics with long histories of maladjustment. The majority have been found to be poor learners as determined by the Army General Classification Tests. Their symptoms have become habitual responses of long standing to conditions of heightened tension, and are apparent usually prior to moments of acute crisis. The difference between these two types of reaction—the one a response of a discouraged but essentially healthy individual to an acute situation, the other a habitual response of a poorly adapted individual to a chronic situation—is carried in the works of Franz Alexander.<sup>5</sup> "A temporary disturbance of any of these (gastro-intestinal) functions may occur in a healthy person under the influence of acute anxiety, rage, distrust or other emotional upheavals. Only when such an emotional disturbance is chronic does one speak of a *gastro-intestinal neurosis*."

The aim of treatment, then, is the prevention of the development of a chronic neurosis in the men of the first group, and the rapid removal to the interior of the men of the second group. The latter step is taken only following consultation with the commanding officer as

to the individual's fitness as a soldier. In passing, it must be admitted that the objection has been raised that the practice of removing these patients to the rear would result in increased numbers of complaints of this type of distress. Actually there was not a single instance where a soldier was suspected of deliberately manufacturing his symptoms. On the contrary, it is felt that the number of known psychoneurotics and incipient psychoneurotics in any large group of soldiers is relatively fixed and that once the poor material has been eliminated the incidence of admissions to the hospital of patients with severe gastro-intestinal neurosis will decrease. This opinion is based upon our experience with a regiment which, during the course of its first eight months overseas, largely eliminated its neurotics, so that when it moved up into an area subject to enemy air activity there were remarkably few admissions for functional disorders of the gastro-intestinal tract. The incidence will not reach the vanishing point, however, because regardless of how careful the screening process, new cases will be bound to arise under conditions of unusual or prolonged stress, even among the "stronger" characters.

#### SUMMARY

1 The gastro-intestinal neuroses are among the commonest forms of psychoneurosis seen in the field.

2 An important but not the sole factor in the incidence of the gastro-intestinal neuroses is the improper selection of soldiers for combat service.

3 Patients with functional disturbances of the gastro-intestinal tract fall into two broad groups: one includes those with mild symptoms of short duration who readily respond to therapy and can be returned to duty; the other those with severe symptoms of longer duration who do not readily respond and have to be returned to the interior for reclassification.

4 The early recognition and treatment of these patients is the most important factor in preventing the establishment of a permanent neurosis.

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